Standard Treatment Guidelines and Essential Medicines List for South Africa

Hospital Level, Adults
2024 Edition

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NOTE:
The information presented in these guidelines conforms to the current medical, nursing and pharmaceutical practice. Contributors and editors cannot be held responsible for errors, individual responses to medicines and other consequences.

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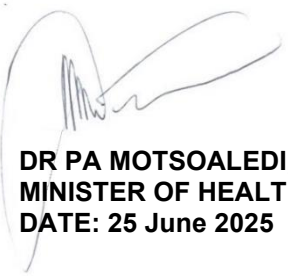
FOREWORD

I proudly present the updated 2024 editions of both the Primary Healthcare (PHC) and Adult Hospital Level (AHL) Standard Treatment Guidelines (STGs) and Essential Medicines List (EML). These guidelines aim to enhance transparency and support the delivery of high-quality treatment options at both PHC and hospital levels. They reflect the evolving clinical needs of our population as well as the introduction of new medicines.

Universal Health Coverage (UHC) aims to eliminate disparities in healthcare access and outcomes, providing financial protection and access to quality healthcare for all South Africans, as mandated by the constitution of South Africa. The National Essential Medicines List Committee (NEMLC) has incrementally increased the use of Health Technology Assessment processes in the selection of essential medicines, providing transparent priority-setting and value-based guidance for efficient resource allocation. The PHC and AHL STGs and EML are a key pillar of UHC, laying the groundwork for structuring health service benefits and ensuring equitable access to safe, effective and affordable medicines for all.

I commend the diligent work of the PHC and AHL Expert Review Committee (ERC), along with the NEMLC, in developing the 2024 editions of the PHC and AHL STGs and EML according to good governance and evidence-based decision principles.

I encourage stakeholders across all sectors to actively participate in the continuous review, development and implementation of these guidelines. I encourage engagement with the NEMLC process of STG development through the external comment process. I appreciate your engagement in presentations and webinars hosted by the NDoH, as well as dissemination of communication published on the National Department of Health web page. Your active involvement is crucial for the successful implementation of these STGs and the improvement of health outcomes for our nation.



DR PA MOTSOALEDI, MP
MINISTER OF HEALTH
DATE: 25 June 2025

INTRODUCTION

The Primary Healthcare (PHC) and Adult Hospital Level (AHL) Standard Treatment Guidelines (STGs) and Essential Medicines List (EML) enable the equitable access to safe, effective and affordable essential medicines across South Africa.

Historically, the PHC and AHL Expert Review Committees (ERCs) responsible for developing the PHC and AHL STGs were appointed as separate Committees. However, in 2020 the Committees were merged to streamline efforts and optimise resources, ensuring a seamless continuum of care between the PHC and AHL of care. The review cycle for these STGs commenced at the onset of the COVID-19 pandemic, necessitating a shift in priorities to address emerging needs and challenges faced by the healthcare system during the pandemic.

The ERC reviews the STGs and EML according to a topic prioritisation framework that includes consideration of clinical need, efficacy, safety, cost-effectiveness, feasibility and equity, presenting recommendations to the National Essential Medicines List Committee (NEMLC) for appraisal and ratification. The multidisciplinary team, which includes clinical experts, clinical pharmacologists and evidence-review and guideline-development methodologists has strengthened the STG development process. The National Department of Health's Essential Drugs Programme team supports this process and has ensured collaboration and alignment with other advisory groups in updating these guidelines.

The NEMLC has incorporated the latest advances in clinical care into various disorder and chapter updates, expanding medicine treatment options including (but not limited to) Blood and Blood-Forming Organs, HIV, Mental Health, Obstetrics and Gynaecology, as well as Palliative Care. Notably, the AHL STGs and EML features a new chapter on Adult Critical Care, developed through extensive consultation across both public and private sectors. This chapter aims to enhance our response capabilities and ensure comprehensive care for critically ill patients.

The 2024 editions of the PHC and AHL STGs and EML reflects the National Department of Health's commitment to continually evolving and enhancing the quality and accessibility of healthcare across our country.

DR SSS BUTHELEZI
DIRECTOR-GENERAL: HEALTH
DATE: 11 June 2025

ACKNOWLEDGEMENTS

This edition of the Adult Hospital Level Standard Treatment Guidelines (STGs) and Essential Medicines List (EML) is evidence of the dedication, technical expertise, skills, and considerable time offered by the combined PHC/Adult Hospital Level Expert Review Committee (ERC) and the National Essential Medicines List Committee (NEMLC). The ERC has enthusiastically evolved with the EML review process, embracing Health Technology Assessment principles as South Africa transitions towards Universal Health Coverage. The dissemination and implementation of these guidelines is greatly encouraged and will ensure equitable access to affordable, good quality essential medicines. We appreciate the continuous participation in the peer review consultative process during the development of this edition of the STGs and EML. We would like to thank each Committee member for their valuable contributions, as well as the Chairpersons of the combined PHC/Adult Hospital Level ERC and NEMLC.

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THE ESSENTIAL MEDICINES CONCEPT

The WHO describes Essential medicines as those that satisfy the priority health care needs of the population. Essential medicines are intended to be available within the context of functioning health systems at all times in adequate quantities, in the appropriate dosage forms, with assured quality and adequate information, and at a price the individual and the community can afford.

The concept of essential medicines is forward-looking. It incorporates the need to regularly update medicines selections to:

» reflect new therapeutic options and changing therapeutic needs;
» the need to ensure medicine quality; and
» the need for continued development of better medicines, medicines for emerging diseases, and medicines to meet changing resistance patterns.

Effective health care requires a judicious balance between preventive and curative services. A crucial and often deficient element in curative services is an adequate supply of appropriate medicines. In the health objectives of the National Drug Policy, the government of South Africa clearly outlines its commitment to ensuring availability and accessibility of medicines for all people. These are as follows:

» To ensure the availability and accessibility of essential medicines to all citizens.
» To ensure the safety, efficacy and quality of medicines.
» To ensure good prescribing and dispensing practices.
» To promote the rational use of medicines by prescribers, dispensers and patients through provision of the necessary training, education and information.
» To promote the concept of individual responsibility for health, preventive care and informed decision-making.

Achieving these objectives requires a comprehensive strategy that not only includes improved supply and distribution, but also appropriate and extensive human resource development. The implementation of an Essential Drugs Programme (EDP) forms an integral part of this strategy, with continued rationalisation of the variety of medicines available in the public sector as a first priority. The private sector is encouraged to use these guidelines and medicine list wherever appropriate.

The criteria for the selection of essential medicines for Adult Hospital Level in South Africa were based on the WHO guidelines for drawing up a national EML. Essential medicines are selected with due regard to disease prevalence, evidence on efficacy and safety, and comparative cost.

The implementation of the concept of essential medicines is intended to be flexible and adaptable to many different situations. It remains a national responsibility to determine which medicines are regarded as essential.

HOW TO USE THESE GUIDELINES

Principles

The National Drug Policy[1] makes provision for an Essential Drugs Programme which is a key component in promoting rational medicines use.

The perspective adopted in the Adult Hospital Level Standard Treatment Guidelines (STGs) is that of a competent medical officer practicing in a public sector hospital. The STGs serve as a standard for practice, but do not replace sound clinical judgment. It is important to remember that the treatments recommended are guidelines only, and are based on the assumption that prescribers can manage patients with the relevant conditions.

This includes rational prescribing in the elderly and palliative care, as the use of some medicines, especially as people get older or more ill, can cause more harm than good. Optimizing medication through targeted de-prescribing is a vital part of managing chronic conditions, avoiding adverse effects and improving outcomes. The goal of de-prescribing is to reduce pill burden, and maintain or improve quality of life.

All reasonable steps were taken to align the STGs with Department of Health guidelines that were available at the time of review. Each treatment guideline in the Adult Hospital Level STGs and Essential Medicines List (EML) was designed as a progression in care from the current Primary Health Care (PHC) STGs and EML. Where referral to a tertiary facility is recommended, the relevant medicines have either been reviewed or included in the tertiary level EML, or are in the process of being reviewed.

Each medicine was included or removed from the EML using an evidence-based review of safety and effectiveness, followed by considerations of cost and other relevant practice factors, such as availability and storage requirements. Some recommendations might not be aligned with the indications or doses included in South African Health Products Regulatory Authority (SAHPRA) approved professional information but are guided by the best available scientific evidence.

The dosing regimens provide the recommended doses used in usual circumstances. However, the prescribed dose should take into consideration drug-drug interactions and co-morbid states, notably renal or hepatic failure, critical illness, and morbid obesity.

Local formularies

A formulary is a continually updated list of medicines and related information on the diagnosis, prophylaxis, or treatment of disease and the promotion of health to satisfy the needs of the majority of the population served by a particular health establishment/s.[2]

[1] National Drugs Policy, 1996. https://www.gov.za/documents/national-drugs-policy
[2] South African National Department of Health. 2022. National Guideline for the Development, Management and Use of Formularies. Pretoria, South Africa.

All EML medicines should be available at the relevant level of care based on the package of services provided at a particular health establishment/s. PTCs should develop formularies aligned to treatment guidelines and protocols subjected to robust evidence-based interrogation and consideration of cost implications.

The EML has been developed to the generic or International Non-Propriety Name (INN) level. Each province, through the provincial PTC, is expected to review the EML and prevailing tenders and compile a formulary which:

» lists formulations and pack sizes that will facilitate care in alignment with the STGs and EML;
» selects the preferred member of a therapeutic class based on cost; and implement formulary restrictions that are consistent with the local environment.

Therapeutic classes are designated in the "Medicine treatment" sections of the STGs, which provide classes of medicines followed by an example of each class, such as 'HMG-CoA reductase inhibitors (statins), e.g., simvastatin'. Therapeutic classes are designated where none of the class members offers any significant benefit over the other registered class members. It is anticipated that by listing a class rather than a specific medicine, there is increased competition and, hence, an improved chance of obtaining the lowest possible price in the tender process. The designation of medicines into therapeutic classes may also assist with remedial actions to mitigate challenges to security of supply, by providing suggested alternatives which have already been approved by the ministerially appointed National Essential Medicines List Committee (NEMLC)[3].

Where therapeutic classes are listed in the STGs, the local formulary should be consulted to identify the specific medicine approved for the facility. A therapeutic interchange database has been developed that lists medicines grouped into a therapeutic class for a specific condition, as outlined in the policy for classifying medicines into therapeutic classes for purposes of therapeutic interchange. The database and policy are available on the National Department of Health website:

https://www.health.gov.za/nhi-hpp-edp/

Navigating the guidelines

It is important that you become familiar with the contents and layout of these guidelines in order to use the STGs effectively.

The STGs are arranged into chapters according to the organ systems of the body. In some therapeutic areas that are not easily amenable to the development of a STG, the section is limited to a list of medicines.

Revisions to previous recommendations are accompanied by the level of evidence that is cited and hyperlinked accordingly. All evidence is graded described in detail

[3] NEMLC is tasked to formulate and revise the Standard Treatment Guidelines (STGs) and Essential Medicines List (EML) using a peer review consultative process.

under Guidelines For The Motivation Of A New Medicine On The National Essential Medicines List. To further promote transparency of medicine selection decisions, NEMLC reports, medicine reviews and costing reports are available on the National

Department of Health website: https://www.health.gov.za/nhi-edp-stgs-eml/ .

The section on Patient Education in Chronic Conditions aims to assist health workers to improve patient adherence and health, generally. Information on the Central Chronic Medicines Dispensing and Distribution (CCMDD) programme is available at: www.health.gov.za/ccmdd.

Diagnosis codes from the International Statistical Classification of Diseases and Related Health Problems (ICD-10) are included for each condition to facilitate the accurate recording of diagnoses. The primary ICD-10 code may be accompanied by a secondary code that is bracketed to differentiate a secondary manifestation from the primary aetiology. (For example, uncomplicated broncho-pneumonia with severe penicillin allergy would be coded as: J18.0+(Z88.0)). All the rules and guidelines for using ICD-10 must be applied as per the World Health Organization (WHO), the agreed South African Morbidity Coding Standards and Guidelines document, and the South African Master Industry Table (MIT).

Available at: **https://www.health.gov.za/icd-10-master-industry-table /**.

Medicines safety

Provincial and local PTCs should develop medicines safety systems to obtain information regarding medication errors, prevalence and severity of adverse medicine events, interactions, and medication quality. These systems should support the regulatory pharmacovigilance plan and provide pharmacoepidemiology data to inform future essential medicine decisions and local interventions to improve safety.

In accordance with the SAHPRA's guidance on reporting adverse drug reactions in South Africa, healthcare workers (with the support of PTCs) should report all relevant adverse reactions to the Pharmacovigilance unit at SAHPRA. The Adverse Drug Reaction form and guidance on its use may be found at the following link: **https://www.sahpra.org.za/document/adverse-drug-reactions-and-quality-problem-reporting-form/**. Additionally, healthcare professionals can report through the Med Safety App. Search for "Medsafety" on the Apple store or Google play store and install the application on your mobile device. The application can also be downloaded onto a smart mobile phone directly from the SAHPRA website, **https://medsafety.sahpra.org.za.**

Feedback

Comments that aim to improve these treatment guidelines will be appreciated. The submission form and guidance for completing the form are included with these guidelines under Guidelines For The Motivation Of A New Medicine On The National Essential Medicines List. Motivations will be accepted from Provincial PTCs only.

These guidelines are also reviewed regularly. During the review process, comments are requested during a comment period and should be forwarded directly to the EML Secretariat. Queries may be submitted to the Essential Drugs Programme via electronic mail to **SAEDP@health.gov.za**.

THERAPEUTIC DRUG MONITORING (TDM)

Medicines with narrow therapeutic indices and those with variable pharmacokinetics should be monitored regularly to optimise dosing, obtain maximum therapeutic effect, limit toxicity, and assess adherence. Appendix II provides detailed information for specific medicines.

TDM sampling for all drugs is usually done only once steady state has been reached (i.e. after 4–5 half-lives), unless there is a specific indication to measure concentrations earlier. Seek the assistance of a clinical pharmacologist if unsure when to perform TDM sampling and how to interpret results.

Lithium

Measure serum concentrations at about 12 hours after the last dose – i.e. immediately prior to the next dose. Concentrations should be less than 1 mmol/L and should be monitored a week after each dose increment, then at one month, three months and 6-monthly[4] while on therapy. More frequent monitoring is indicated in the elderly (see Appendix II for guidance on prescribing lithium).

Aminoglycosides

Aminoglycoside TDM is not necessary when the course of extended-interval aminoglycoside dosing is not expected to exceed 3 days in patients with normal renal function. Trough concentrations, taken immediately before the next dose, are critical for identifying potential toxicity. Peak concentrations are taken 30 minutes to 1 hour after starting the infusion and are used to determine if the dose is adequate for efficacy. Toxicity may manifest as deafness or renal impairment. Aminoglycosides are relatively contraindicated in renal impairment. Bedside hearing assessment and renal function monitoring is indicated in all patients treated with aminoglycosides longer than 3 days (see Appendix II for

[4] South African Medicines Formulary, 14th Edition. Division of Clinical Pharmacology. University of Cape Town, 2022.

guidance on prescribing amikacin and gentamicin). Urgent referral for formal audiology testing may be warranted if bedside hearing tests are abnormal.

Anti-epileptics

Measuring concentrations may be helpful to confirm poor adherence or to confirm a clinical suspicion of toxicity. Routine measurement in patients with well-controlled seizures and no clinical evidence of toxicity is not appropriate.

PRESCRIPTION WRITING

Prescribers may initiate and/or maintain treatment with medicines as per the STGs in accordance with their scope of practice.

Medicines should be prescribed only when they are necessary for treatment following clear diagnosis. Not all patients or conditions need prescriptions for medication. In certain conditions simple advice and general and supportive measures may be more suitable.

In all cases carefully consider the expected benefit of a prescribed medication against potential risks. This is especially important during pregnancy where the risk to both mother and fetus must be considered.

All prescriptions must:

» be written legibly in ink OR typed, and printed OR entered electronically, where such systems exist by the authorised prescriber, and signed with the date on the prescription form (NOTE: only advanced electronic signatures are acceptable, and require access to specific software packages);
» include the full name, identification number and address of the patient;
» specify the age and, in the case of children, the weight of the patient;
» have prescriber details, including contact details, i.e., name, qualification, registration and/or practice number, address and contact telephone number;
» indicate the diagnosis on the prescription, where the patient has provided consent.

In all prescriptions:

» State the treatment regimen in full:
  - medicine name (preferably the generic name or INN), strength and formulation,
  - dose,
  - dose frequency,
  - route of administration,
  - duration of treatment,
  - e.g., amoxicillin 250 mg capsules, 8 hourly orally for 5 days.
» Write the name of the full medicine/preparation using the generic name.
» Avoid abbreviations to reduce the risk of misinterpretation. Avoid the Greek mu (ų): write mcg as an abbreviation for micrograms.
» Avoid unnecessary decimal point use. If necessary, write a zero in front of the decimal point only, e.g., 2 mg, not 2.0 mg, or 0.5 mL, not .5 mL.
» Avoid Greek and Roman frequency abbreviations that cause considerable confusion (qid, qod, tds, tid, etc). Instead, state the frequency in terms of hours

(e.g., ‘8 hourly’) or times per day in numerals (e.g., ‘3x/d’).
» In the case of “as required”, a minimum dose interval should be specified, e.g., ‘every 4 hours as required’.
» Most monthly outpatient prescriptions for chronic medication are for 28 days; check that the patient can access a repeat before the 28 days are completed. Repeats may be issued for Schedule 0 to 5 medicines for up to 6 months.
» Prescriptions for Schedule 6 medicines are not repeatable and are to be issued monthly; the quantity should be expressed in words.

After writing a prescription, check that each item's dose, dose units, route, frequency, and duration are stated. Consider whether the number of items is too great to be practical for the patient, and check that there are no redundant items or potentially important drug interactions. Check that the prescription is dated and that the patient’s name, identification number and diagnosis/diagnostic code are on the prescription form. Only then should you sign the prescription and provide another way for the pharmacy staff to identify the signature if there are problems (print your name, use a stamp, or use a prescriber number from your institution’s pharmacy).

SECTION 21 ACCESS TO UNREGISTERED MEDICINES

Section 21 of the Medicines and Related Substances Act, 1965 (Act 101 of 1965) as amended, allows access to unregistered medicines. The enabling provision in the Act reads as follows:

21. Authority may authorize sale of unregistered medicines, medical devices or in vitro diagnostics (IVDs) for certain purposes:
(1) The Authority may in writing authorize any person to sell during a specified period to any specified person or institution a specified quantity of any particular medicine, medical device or IVD which is not registered.

(2) Any medicine, medical device or IVD sold in pursuance of any authority granted under subsection (1) may be used for such purposes and in such manner and during such period as the Authority may in writing determine.

(3) The Authority may at any time by notice in writing withdraw any authority granted in terms of subsection (1) if effect is not given to any determination made in terms of subsection (2).

The Act needs to be read together with the relevant General Medicines Regulation and the guidelines issued by the South African Health Products Regulatory Authority (SAHPRA). General Regulation 29 lists the details that must be included in a Section 21 application and also the obligations placed on the person under whose supervision the unregistered medicine is prescribed. Two guidelines are relevant in this regard:

- SAHPGL-CEM-S21-02 Guideline For Section 21 Access To Unregistered Medicines5 (accessible at

[5] South African Health Products Regulatory Authority. Guideline For Section 21 Access to Unregistered Medicines. 5 September 2022.

https://www.sahpra.org.za/document/guideline-for-section-21-access-to-unregistered-medicines/).

- SAHPGL-PEM-01 Availability of medicines for use in a Public Health Emergency6 (PHE) (accessible at https://www.sahpra.org.za/document/availability-of-medicines-for-use-in-a-public-health-emergency-phe/).

Application for Section 21 approval has to be made via the online portal, at https://www.sahpra.org.za/e-services, then navigate to "Section 21 Applications"

For further information about section 21 procedures, see https://www.sahpra.org.za/category-a-unregistered-products/

The SAHPRA guidelines envisage five possible scenarios:

1. Individual named patient - where access to an unregistered medicine is required for an individually named patient when conventional therapies have failed in such cases, the application is made by an individual health care provider responsible for the care of the patient. In addition, a co-applicant is needed, which is the licensed manufacturer/importer/distributor responsible for the supply of the product for which authorisation is requested.

2. Bulk stock held by a health establishment - where an unregistered medicine needs to be available urgently and an individually named patient application is not possible. In such cases, the applicant will be the health care provider who is the intended prescriber of such medicine or a health care provider who is designated as a representative of the health establishment requiring the stock. A co-applicant also needs to be identified.

3. Bulk stock held by the holder of a licence issued in terms of section 22C(1)(b) – where a licensed distributor needs to maintain stock of a particular unregistered medicine at a single point of storage for distribution on an urgent basis to one or more health care providers or health establishments.

4. State Procurement – where an unregistered medicine may need to be procured by the State for distribution on an urgent basis to one or more public sector health establishments, when all other mechanisms of supply have been exhausted and where, without intervention, a significant public health risk may be realised. In such cases, the State may designate a health care provider as a representative in order to apply for authorisation for the supply or sale of an unregistered medicine to, and by health establishments. The co-applicant will also have to be identified.

5. Public health emergency (PHE) – where access is needed to an unregistered medicine in order to respond to an extraordinary event which poses a serious health risk to the public or has caused or has the potential to cause an outbreak, epidemic or pandemic.

[6] South African Health Products Regulatory Authority. Availability Of Medicines for Use in A Public Health Emergency (PHE). August 2023.

Applications in terms of scenario 1 can be made by individual prescribers in the public health sector, with the approval of the responsible Pharmaceutical and Therapeutic Committee. Applications in terms of scenario 2 would ordinarily be done at a provincial or national level. Applications in terms of scenario 4 should preferably be done at a national level, unless the unregistered medicine is only required in a specific province. Applications in terms of scenario 5 would require national decisions to activate the specific guidance.

Although a separate section 21 application is not required, approval of a clinical trial by SAHPRA includes an implicit approval for importation of an unregistered investigational agent. The reporting requirements for clinical trials are also specific to that scenario.

Notes on specific medicines

ACE-inhibitor	Angioedema is a potentially serious complication of ACE- inhibitor treatment and if it occurs it is a contraindication to continued therapy or to re-challenge.
ACE-inhibitors and angiotensin receptor blockers (ARBs)	ACE-inhibitors and ARBs can cause or exacerbate hyperkalaemia in chronic kidney disease (eGFR < 60 mL/minute). Check the serum potassium before starting these medicines, and monitor serum potassium on therapy. ACE-inhibitors and ARBs are contra-indicated in pregnancy. In impaired kidney function: GFR 10–50 mL/min, 50–100% of dose; GFR <10 mL/min, 25% of dose.
Allopurinol	Contra-indicated in patients with eGFR < 30 mL/minute. Do not stop uric acid lowering drugs during an acute attack. In impaired kidney function reduce dose to avoid toxicity. Creatinine clearance 10–20 mL/min, 100–200 mg/day; <10 mL/min, 100 mg/day or at longer intervals.
Amitriptyline + citalopram	Concomitant use of amitriptyline and citalopram may increase the risk of serotonin syndrome or neuroleptic malignant syndrome. Furthermore, there is a potential risk for QT- prolongation.
Anti-epileptic medicines	Phenytoin, phenobarbitone, and carbamazepine are potent enzyme inducing agents and should be used with caution with other medicines metabolised by the liver, especially warfarin, antiretrovirals, progestin subdermal implants, and oral contraceptives.
Antivenom	Never administer antivenom without being fully prepared to manage acute anaphylaxis.

Benzodiazepines	Benzodiazepines can cause respiratory depression. Monitor patients closely as benzodiazepines can exacerbate an abnormal mental state or mask important neurological signs of deterioration. Prolonged treatment with benzodiazepines often leads to tolerance and withdrawal symptoms if the medicine is discontinued abruptly. Combination therapy with more than one benzodiazepine is not indicated.
ß–blockers	ß–blockers should not be used in cocaine poisoning. ß–blockers may cause bronchospasm in asthmatics.
Calcineurin inhibitors	Both tacrolimus and ciclosporin may cause hyperglycaemia, hypertension, hyperlipidaemia, neurotoxicity, and nephrotoxicity. Ciclosporin may also cause hirsutism and gingival hyperplasia. Both tacrolimus and ciclosporin are prone to multiple drug-drug interactions and concomitant medications should be reviewed. Renal function, liver function, serum electrolytes, blood glucose, total cholesterol, and blood pressure should be monitored regularly on treatment. Therapeutic drug monitoring of trough concentrations of ciclosporin and tacrolimus should be used to guide dose adjustment, maintain therapeutic efficacy, and avoid toxicity.
Clindamycin	Clindamycin has good coverage against Gram positive organisms and anaerobes, so the addition of metronidazole is unnecessary.
Diuretics	Hydrochlorothiazide is contraindicated when anuric or GFR < 10 mL/minute.[7,8]
Folic acid + vitamin B12	Anaemia megaloblastic: Give vitamin B12 and folic acid together until the test results are available as giving folic acid alone in patients with a B12 deficiency may precipitate a permanent neurological deficit.
Haloperidol	Dosing may vary according to clinical circumstances, e.g. lower doses in the elderly or where HIV infection or HIV-related dementia is known or suspected. In frail and elderly patients, reduce the dose by half.
Lithium	Therapeutic drug monitoring is essential when using lithium. Clinical toxicity may occur even within the therapeutic range. Concomitant use of many medicines

[7] Sinha AD, Agarwal R. Clinical pharmacology of antihypertensive therapy for the treatment of hypertension in CKD. Clin J Am Soc Nephrol. 2019;14(5):757-764. doi:10.2215/CJN.04330418 [PubMed 30425103]
[8] Aronoff GR. Drug Prescribing in Renal Failure: Dosing Guidelines for Adults. 4th ed. Philadelphia, Pa.: American College of Physicians, 1999

	e.g. ACE-inhibitors, ARBs, NSAIDs and diuretics may increase the risk of lithium toxicity.
Loperamide	Contraindicated in dysentery, acute inflammatory diarrhoea, antibiotic-associated diarrhoea and amoebic dysentery; as it may result in toxic megacolon
Low molecular weight heparin (LMWH)	In morbid obesity dosing of LMWH should be individualised, in discussion with a specialist. In renal failure (eGFR < 30 mL/minute), the recommended dose of LMWH is 1 mg/kg/day. Pregnant women with mechanical prosthetic valves should not receive LMWH unless antifactor Xa levels can be monitored reliably weekly. Therapeutic range is pre-dosing level of 0.6 units/mL and a 4-hour peak level of 1–1.2 units/mL.
Metformin	Metformin should be dose-adjusted if eGFR: 30-60 mL/minute and should not be used if eGFR: < 30mL/minute). Co-administration with Dolutegravir may increase metformin concentration, limit the dose of metformin to ≤ 2g per day if concomitant use with Dolutegravir.
Metronidazole	Adding metronidazole to amoxicillin/clavulanic acid is unnecessary as amoxicillin/clavulanic acid has adequate anaerobic cover.
Misoprostol (for Termination Of Pregnancy)	Misoprostol can cause uterine rupture in women with previous caesarean sections and those of high parity. In these women use 200 mcg of misoprostol or alternative methods such as extra-amniotic saline infusion without misoprostol. The dose of misoprostol, PV, decreases with increasing gestational age because of the risk of uterine rupture.
Non-steroidal anti-inflammatory drugs (NSAIDs)	Concomitant use of more than one NSAID has no additional clinical benefit and only increases toxicity. Chronic use of all NSAIDs is associated with varying degrees of gastrointestinal, renal, and cardiovascular risks. Long-term use of NSAIDs should weigh potential benefits against these risks.
Oral antidiabetic agents	Oral antidiabetic agents (sulfonylureas) should not be used in type 1 diabetes and used with caution in liver and renal impairment.
Insulin in the treatment of diabetic ketoacidosis (DKA)	Potassium will fall on insulin treatment and patients with DKA have potassium depletion even if initial potassium is normal or high. It is therefore essential to monitor and replace potassium.
Fluoroquinolones	Irrational use of fluoroquinolones contributes to the emergence of XDR-TB and potential masking of active TB.
Sodium chloride	Rapid correction of sodium, in hyponatraemia, may lead to central pontine myelinolysis, which is often irreversible. Sodium should be frequently monitored and increases should be <9 mmol/L per day.

Spironolactone	Monitoring of sodium, potassium and renal function is essential in patients taking spironolactone. Avoid if eGFR < 30 mL/minute.
Selective serotonin reuptake inhibitors (SSRIs)	Adolescents with depression may have an increased risk of suicidal ideation when initiated on SSRIs.
Streptokinase	Do not use heparin if streptokinase is given.
Sulphonylureas	Hypoglycaemia caused by a sulphonylurea can be prolonged. The patient should be hospitalised with an intravenous glucose infusion, and observed for at least 12 hours after glucose infusion has stopped.
Tricyclic antidepressants	Avoid in patients with cardiac disease and a high risk of overdose.
Testosterone	Screen hypogonadal men for prostate cancer before beginning testosterone replacement.
Unfractionated heparin	Evidence indicates that PTT monitoring is not necessary with weight-based dosing of unfractionated heparin. However, in patients with morbid obesity and renal failure (eGFR < 30 mL/minute) unfractionated heparin should be used with PTT monitoring to maintain the PTT at 1.5 to 2.5 times the control. Blood for measurement of PTT should be taken 4 hours after SC dose.
Verapamil	Never give verapamil or adenosine IV to patients with a wide QRS tachycardia as this may precipitate ventricular fibrillation. In atrial flutter, do not use verapamil as it will not convert flutter to sinus rhythm and may cause serious hypotension.
Warfarin	Warfarin use requires regular INR monitoring and dose adjustment according to measured INR. See appendix II.

PENICILLIN DESENSITISATION

This has been included for information only.

Perform only in an ICU setting or in a setting where recognition and management of anaphylaxis can be assured.

Discontinue all ß-adrenergic antagonists. Have an IV line, ECG monitor and spirometer in place. Once desensitised, treatment must not lapse as risk of subsequent allergy increases.

A history of Stevens-Johnson's syndrome, exfoliative dermatitis, erythroderma are absolute contra-indications to desensitisation (use only as an approach to IgE sensitivity).

Oral route is preferred. 1/3 of patients develop a transient reaction during desensitisation or treatment, which is usually mild.

Oral penicillin desensitisation protocol

A: Prepare stock solution of oral phenoxymethylpenicillin 250mg/ 5mL and dilutions for steps 1-7 and 8-10 B: Administer increasing doses of penicillin strictly at 15 minutes intervals		
Step	**Medicine mg/mL**	**Amount to administer (mL)**
To make 0.5 mg/mL solution: Add 0.5 mL of stock phenoxymethylpenicillin solution to 49.5 mL water (total volume 50mL)		
1	0.5 mg/mL solution (1000 units/mL)	0.1 mL orally
2		0.2 mL orally
3		0.4 mL orally
4		0.8 mL orally
5		1.6 mL orally
6		3.2 mL orally
7		6.4 mL orally
To make 5 mg/mL solution: Dilute 1 mL of stock phenoxymethylpenicillin solution with 9 mL water (total volume 10mL)		
8	5 mg/mL solution (10000 units/mL)	1.2 mL orally
9		2.4 mL orally
10		4.8 mL orally
Stock phenoxymethylpenicillin 250 mg/5 mL = 50 mg/mL		
11	50 mg/mL (80000 units/mL)	1.0 mL orally
12		2.0 mL orally
13		4.0 mL orally
14		8.0 mL orally

After step 14, observe for 30 minutes, then administer desired dose of intravenous penicillin.

Intravenous penicillin desensitisation protocol

A. Prepare stock solution for intravenous administration of benzathine penicillin G of 100mg/ml and dilutions for steps 1-5, 6-8, and 9-12. Label dilutions carefully.
Use 600mg vial =1MU

a. reconstitute dry powder with 6mls water for injection to make stock of 100mg/ml (steps 13-16)
b. Take 1ml of 100mg/ml stock and reconstitute with 9ml to make a 10mg/ml solution (steps 9-12)
c. Take 1ml of 10mg/ml benzathine penicillin G and reconstitute with 9mLs water to make a 1mg/ml solution (steps 6-8)
d. Take 1ml of 1mg/ml benzathine penicillin G and reconstitute with 9mLs water to make a 0.1mg/ml solution (steps 1-5)

B. Administer increasing doses of penicillin **strictly at 15 minutes intervals**

Step	Medicine (mg/ml)	Volume to administer (ml)	Route Cumulative dose (mg)
Use 0.1 mg/mL solution			
1	0.1	0.1	0.01
2	0.1	0.2	0.03
3	0.1	0.4	0.07
4	0.1	0.8	0.15
5	0.1	1.6	0.31
Use 1mg/ml solution			
6	1	0.32	0.63
7	1	0.64	1.27
8	1	1.2	2.47
Use 10mg/ml solution			
9	10	0.24	4.87
10	10	0.48	10
11	10	1	20
12	10	2	40
Use 100mg/ml stock solution			
13	100	0.4	80
14	100	0.8	160
15	100	1.6	320
16	100	3.2	640

Cumulative dose of 640mg (1MU) given on completion of step 16. Observe the patient for 30 minutes and then administer the full therapeutic dose intravenously.

COTRIMOXAZOLE DESENSITISATION

Attempt desensitisation in patients with a history of cotrimoxazole intolerance, unless this was life-threatening, e.g.: Stevens-Johnson syndrome. (See section 4 . 6 : Erythema Multiforme, Stevens Johnson Syndrome, Toxic Epidermal Necrolysis).). If a rash occurs during cotrimoxazole treatment, assess severity and discontinue treatment if the rash is severe or associated with systemic symptoms. For mild rashes, treatment may be continued with careful observation for deterioration. Desensitisation should be attempted using cotrimoxazole suspension 240 mg/5mL. Dilute the suspension appropriately and consult with your pharmacist if necessary.

Note: Do not administer antihistamines or steroids with this regimen.

The following protocol describes a simple approach for cotrimoxazole desensitization.

Use cotrimoxazole suspension 240mg/5ml.

Desensitisation must be conducted in hospital and should be done WITHOUT antihistamine or steroid cover.

Take 1ml co-trimoxazole suspension (240mg/5ml) and dilute to 1litre with water and shake very well (mixture A)

Now take 1ml of mixture A and dilute with water to 10ml. (mixture B).

Time	Dose	Dose in mls of undiluted cotrimoxazole suspension
Time 0	Administer 5ml of mixture B. **(Discard balance of mixture B)**	0.0005
Time 1hr	Administer 5ml of mixture A (after shaking well)	0.005
Time 2hr	Administer 50ml of mixture A (after shaking well) **(Discard balance of mixture A)**	0.05
Time 3hr	Administer 0,5ml of co-trimoxazole suspension diluted to 5ml with water	0.5
Time 4hr	Administer 5ml of cotrimoxazole suspension	5.0
Time 5hr	Administer 2 single strength (80/400mg) cotrimoxazole tablets	
Time 6hr	Start full-dose cotrimoxazole	

Medicines Information Centre, Division of Pharmacology University of Cape Town Faculty of Health Sciences

A GUIDE TO PATIENT ADHERENCE IN CHRONIC CONDITIONS

Achieving health goals for chronic conditions such as asthma, diabetes, HIV and AIDS, epilepsy, hypertension, mental health disorders and TB requires attention to:

» Adherence to long term pharmacotherapy – incomplete or non-adherence can lead to failure of an otherwise sound pharmacotherapeutic regimen.
» Organisation of health care services, which includes consideration of access to medicines and continuity of care.

Patient Adherence

Adherence is the extent to which a person's behaviour – taking medication, following a diet and/or executing lifestyle changes, corresponds with agreed recommendations from a health care provider.

Poor adherence results in less than optimal management and control of the illness and is often the primary reason for suboptimal clinical benefit. It can result in medical and psychosocial complications of disease, reduced quality of life of patients, and wasted health care resources.

Poor adherence can fall into one of the following patterns where the patient:

» takes the medication very rarely (once a week or once a month);
» alternates between long periods of taking and not taking their medication e.g. after a seizure or BP reading;
» skips entire days of medication;
» skips doses of the medication;
» skips one type of medication;
» takes the medication several hours late;
» does not stick to the eating or drinking requirements of the medication;
» adheres to a purposely modified regimen; and
» adheres to an unknowingly incorrect regimen.

Adherence should be assessed on a regular basis. Although there is no gold standard, the current consensus is that a multi method approach that includes self-report be adopted such as that below.

Barriers that contribute toward poor adherence:

BARRIER	RECOMMENDED SUPPORT
Life style	
» It is often difficult to take multiple medications.	» Create a treatment plan with information on how and when to take the medications.
» A busy schedule makes it difficult to remember to take the medication.	» Use reminders such as cues that form part of the daily routine.
Attitudes and beliefs	
» The condition is misunderstood or denied.	» Remind patients that they have a long term illness that requires their involvement.
» Treatment may not seem to be necessary.	» Use change techniques such as motivational interviewing.
» May have low expectations about treatment.	» Identify goals to demonstrate improvement/stabilisation.
Social and economic	
» May lack support at home or in the community	» Encourage participation in treatment support programs.
» May not have the economic resources to attend appointments.	» Consider down referral or reschedule appointment to fit in with other commitments.
Healthcare team related	
» Little or no time during the visit to provide information.	» Encourage patient to ask questions.
» Information may be provided in a way that is not understood.	» Use patient literacy materials in the patient's language of choice.
» Relationship with the patient may not promote understanding and self-management.	» Engage active listening.
Treatment related	
» Complex medication regimens (multiple medications and doses) can be hard to follow.	» If possible reduce treatment complexity
» May be discouraged if they don't feel better right away.	» Help the patient understand the condition and the role of their medication
» May be concerned about adverse effects.	» Discuss treatment goals in relation to potential adverse effects.

Although many of these recommendations require longer consultation time, this investment is rewarded many times over during the subsequent years of management.

For a patient to consistently adhere to long term pharmacotherapy requires integration of the regimen into his or her daily life style. The successful integration of the regimen is informed by the extent to which the regimen differs from his or her established daily routine. Where the pharmacological proprieties

of the medication permits it, the pharmacotherapy dosing regimen should be adapted to the patient's daily routine. For example, a shift worker may need to take a sedating medicine in the morning when working night shifts, and at night, when working day shifts. If the intrusion into life style is too great alternative agents should be considered if they are available. This would include situations such as a lunchtime dose in a school-going child who remains at school for extramural activity and is unlikely to adhere to a three times a regimen but may very well succeed with a twice daily regimen.

Towards concordance when prescribing

Establish the patient's:

» occupation,
» daily routine,
» recreational activities,
» past experiences with other medicines, and
» expectations of therapeutic outcome.

Balance these against the therapeutic alternatives identified based on clinical findings. Any clashes between the established routine and life style with the chosen therapy should be discussed with the patient in such a manner that the patient will be motivated to change their lifestyle.

Note: Education that focuses on these identified problems is more likely to be successful than a generic approach toward the condition/medicine.

Education points to consider

» Focus on the positive aspects of therapy, but be supportive regarding negative aspects and offer guidance on how to manage this, if present.
» Provide realistic expectations regarding:
  – normal progression of the illness - especially important in those diseases where therapy merely controls the progression and those that are asymptomatic;
  – the improvement that therapy and non-medicinal treatment can add to the quality of life.
» Establish therapeutic goals and discuss them openly with the patient.
» Any action to be taken with loss of control or when side effects develop.
» In conditions that are asymptomatic or where symptoms have been controlled, reassure the patient that this reflects therapeutic success, and not that the condition has resolved.
» Where a patient raises concern regarding anticipated side effects, attempt to place this in context with respect to incidence, the risks vs. the benefits, and whether or not the side effects will disappear after continued use.

Note: Some patient's lifestyles make certain adverse responses acceptable which others may find intolerable. Sedation is unlikely to be acceptable to a student, but an older patient with insomnia may welcome this side effect. This is where concordance plays a vital role.

Notes on prescribing in chronic conditions.

» Do not change doses without good reason.
» Never blame anyone or anything for non-adherence before fully investigating

the cause.

» If the clinical outcome is unsatisfactory - investigate adherence (note that side effects may be an issue).
» Always think about side effects and screen for them from time to time.
» When prescribing a new medicine for an additional health related problem ask yourself whether or not this medicine is being used to manage a side effect.
» Adherence with a once daily dose is best. Twice daily regimens show agreeable adherence. However, adherence decreases as the number of administration interval increases.
» Keep the total number of tablets to an absolute minimum as too many may lead to medication dosing errors and may influence adherence.

Improving Continuity of Therapy

» Make clear and concise records.
» Involvement the patient in the care plan.
» Every patient on chronic therapy should know:
  – his/her diagnosis
  – the name of every medicine
  – the dose and interval of the regimen
  – his/her BP or other readings

  Note: The prescriber should reinforce this only once management of the condition has been established.
» When the patient seeks medical attention for any other complaints such as a cold or headache he/she must inform that person about any other condition/disease and its management.
» If a patient indicates that he/she is unable to comply with a prescribed regimen, consider an alternative - not to treat might be one option, but be aware of the consequences e.g. ethical.

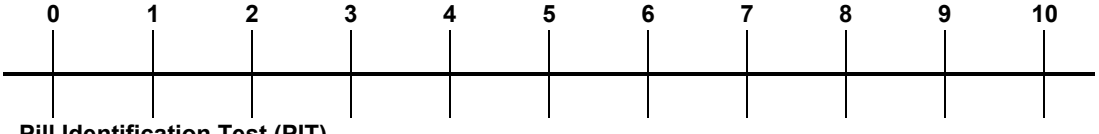
Patient Adherence Record

Folder No.	Date (dd/mm/yyyy) / /

Self-Reporting

Question	**Yes**	**No**
Do you sometimes find it difficult to remember to take your medicine?		
When you feel better, do you sometimes stop taking your medication?		
Thinking back over the past four days, have you missed any of your doses?		
Sometimes if you feel worse when you take the medicine, do you stop taking it?		

Visual Analogue Scale (VAS)



Score ____%

Pill Identification Test (PIT)

Medication	Knows the name (Y/N)	Knows the number of pills per dose (Y/N)	Time the medication is taken			Knows any additional instruction
			Morning (hour)	Evening (hour)	Considered Acceptable (Y/N)	

Pill Count

Did the client return the medication containers? Yes* No

If yes, check that the client only used medication from this container since the date of their last visit. If leftover medication had been used or an emergency prescription obtained, then the calculation will be invalid – skip to adherence assessment.

% Adherence = (**Dispensed** – **Returned**) / **Expected to be taken** **X 100 =** (☐ – ☐) / ☐ **X 100 =** ☐ **%**

Adherence Assessment

Self-reporting	Answered 'No' to all questions	Answered 'Yes' to 1 question	Answered 'Yes' to 2 or more questions
VAS	≥ 95%	75–94%	Less than 75%
PIT—*Client knows the…*	Dose, Time, and Instructions	Dose and Time	Dose only or confused
Pill count	≥ 95%	75–94%	Less than 75%
Overall Adherence	High	Moderate	Low

CENTRAL CHRONIC MEDICINE DISPENSING AND DISTRIBUTION (CCMDD)/DABLAPMEDS

Shortcut to your chronic meds®

dablapmeds
The shortcut to your chronic medication

The Central Chronic Medicines Dispensing and Distribution programme (CCMDD)Dablapmeds, an innovation has been implemented to improve alternative access to chronic medicines for stable patients. with chronic conditions. Patients choose to collect their multimonth repeat medicines at a contracted pick-up point nearer to home or place of work. It is free, safe, convenient and no out of pocket payment. and it is no longer necessary to wait in long queues at health facilities just to collect repeat medicines.

Each province provides a list of medicines aligned to the EML and STGs including prescriber levels that can be utilised for recruitment of patients on the programme. Prescriptions for patients enrolled on CCMDD not meeting legal requirements and compliance to EML and STGs are rejected. The ultimate goal of the CCMDD programme is to improve adherence and better health outcomes.

CCMDD Benefits:

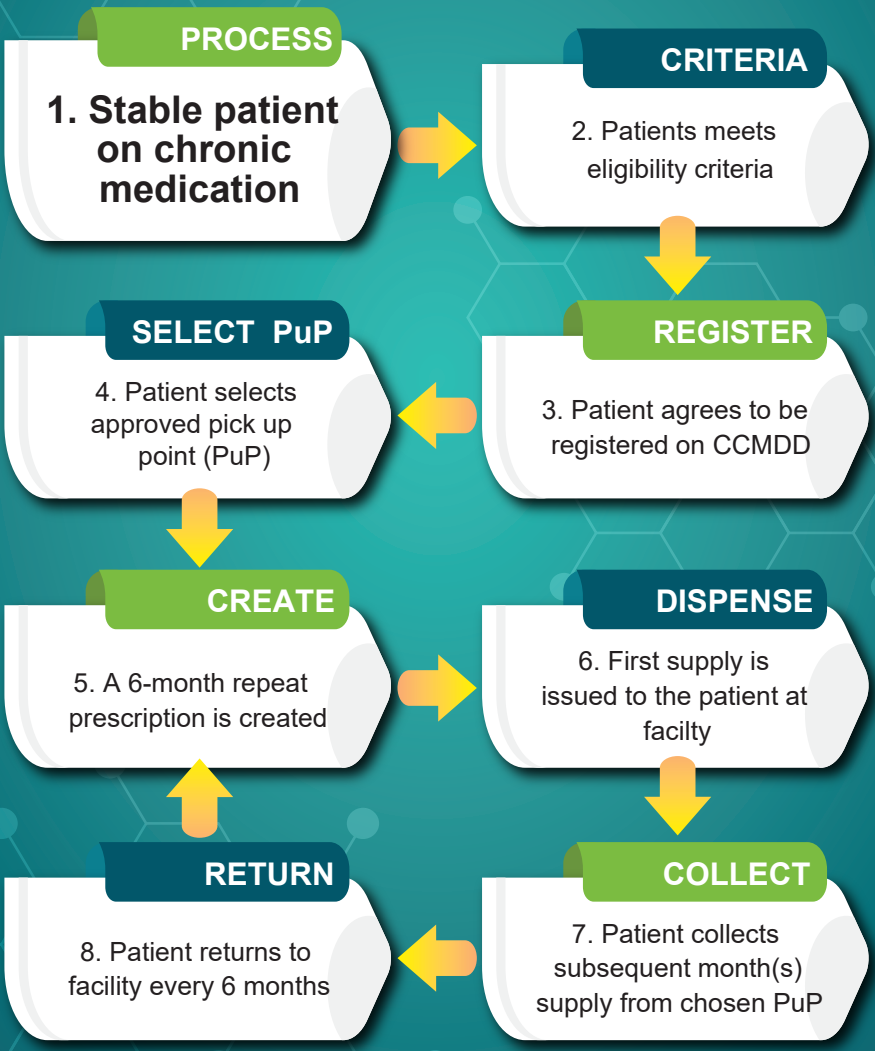
Improved **access** to chronic medicines;
Improved **quality** of care and service delivery;
Improved **patient experience** in the collection of chronic medication;
Improved treatment **adherence**;
Improved **supply chain** processes;
Improved availability of reliable **data** to inform decision-making at:
- Facilities, Service Providers, Pick up Points

Decreased **stigma** for HIV patients;
Reduced **workload** for public health facilities and healthcare workers;
Reduced patient **waiting times** and better time management;
Decongestion of health facilities through the use of alternative Pick up Points;

“CCMDD is a proven, successful, patient centric approach to service patients in a manner that is beneficial to patients, Departments of Health, communities and creates lasting partnerships with the private sector.”

Detailed information regarding the CCMDD process can be accessed at:
WWW.HEALTH.GOV.ZA/CCMDD

Central Chronic Medicine Dispensing and Distribution (CCMDD)



AWaRe Classification of Antibiotics

BACKGROUND

The World Health Organization (WHO) has categorised antibiotics into three groups based on their potential to induce and propagate resistance. This grouping is also used to identify antibiotics that are priorities for monitoring and surveillance.

Most medicines remain effective even if used by many people for prolonged periods. Unfortunately, antibiotics are an important exception as they can become ineffective because of anti-microbial resistance.

ANTIMICROBIAL RESISTANCE

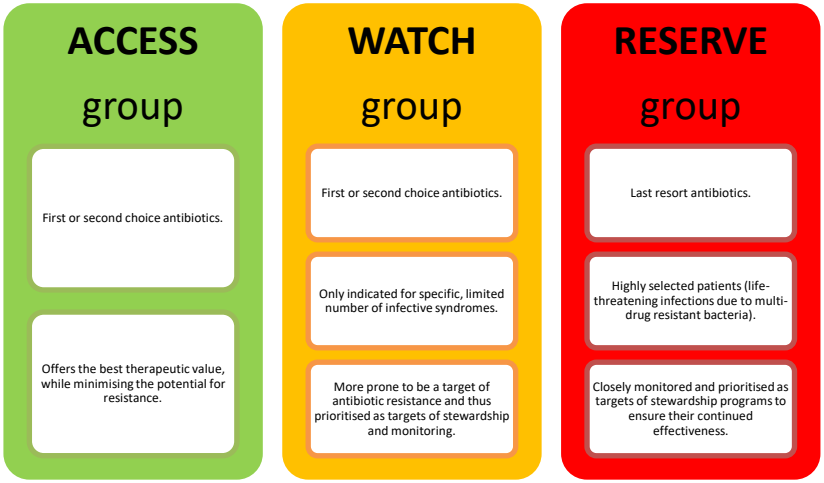
Antibiotic resistance refers to the ability of microorganisms to withstand the effects of an antibiotic.

Bacteria are said to develop resistance when they are no longer inhibited or killed by a given antibiotic.

Inappropriate use of antibiotics favours the emergence and spread of antibiotic resistance, amplifying natural ability of bacteria to resist.
In order to keep antibiotics effective, we need to take them only when needed and strictly as directed by the prescriber / healthcare professional

Furthermore, there is a need to select the right antibiotic for a given infection when they are needed. Those antibiotics that offer the best therapeutic advantage while minimizing the risk of resistance should be privileged.

The aim of the WHO AWaRe antibiotic categorization is to provide a tool to use antibiotics safely and effectively.



These groups have been highlighted in the Standard Treatment Guidelines with the following graphics:

A Indicates that this antibiotic falls within the Access group.

W Indicates that this antibiotic falls within the Watch group.

R Indicates that this antibiotic falls within the Reserve group.

Further information on the AWaRe categorisation, and for a full list of all antibiotics and which category they fall into, can be found at: https://aware.essentialmeds.org/groups.

CHAPTER 1
ALIMENTARY TRACT

1.1 GASTROINTESTINAL DISORDERS

1.1.1 BOWEL PREPARATIONS

DESCRIPTION
Bowel preparation is essential for colonoscopy. LoE:IIa[i]

GENERAL MEASURES
Health care professionals should provide both oral and written patient education instructions and emphasise the importance of adherence to the bowel preparation.

MEDICINE TREATMENT
Start bowel preparation as a split-dose regimen the day before the scheduled procedure: half the dose the night before and half the dose on the day of colonoscopy.
Commence a low residue diet the day before.

Preparations containing ingredients such as polyethylene glycol (PEG) and sodium sulfate are adequate for bowel cleansing. LoE:II[ii]

- PEG/sodium sulfate oral, solution:
  - Prescribe 2 litres the night before the procedure and 2 litres the following morning, two hours prior to the procedure. LoE:I[iii]

Note:
Routine use of adjunctive agents (e.g. bisacodyl, senna, prokinetics) for bowel cleansing before colonoscopy is not recommended. LoE:III[iv]

1.1.2 DIVERTICULOSIS
K57.0-5/K57.8-9

DESCRIPTION
Colonic diverticulosis becomes increasingly common with age. Acute diverticulitis is suspected in patients with lower abdominal pain (typically in the left lower quadrant). The pain is usually constant and is often present for several days prior to presentation. Nausea and vomiting are often present due to a bowel obstruction or an ileus as a result of peritoneal irritation. This may be associated with changes in bowel habits.

Diverticulosis can be complicated by haemorrhage or diverticulitis. Acute diverticulitis is inflammation of diverticulae and may, uncommonly, be accompanied by polymicrobial infection. Acute diverticulitis is defined as complicated in the presence of bowel obstruction, abscess, fistula, or perforation.

GENERAL MEASURES
Increase dietary fibre intake.

MEDICINE TREATMENT
Not all patients require antibiotics. If antibiotic treatment is required, the total duration is ten days depending on clinical response.

Uncomplicated diverticulitis:

- Amoxicillin/clavulanic acid, oral, 875/125 mg 12 hourly. A

LoE:III[V]

If unable to tolerate oral therapy:

- Amoxicillin/clavulanic acid, IV, 1.2 g 8 hourly. A
  - Switch to oral therapy once able to tolerate.

REFERRAL
» Acute diverticulitis with clinical deterioration or failure to improve on medical therapy.
» Peritonitis.
» Complicated diverticulitis (to a centre which can perform colonic surgery).
» Massive haemorrhage.

1.1.3 GASTRO-OESOPHAGEAL REFLUX DISEASE (GORD) AND DYSPEPSIA
K21.0/K21.9/K22.7/K30

DESCRIPTION
GORD is a disorder which develops as a consequence of the reflux of gastric and duodenal contents into the oesophagus. It is usually characterised by heartburn and regurgitation.

Dyspepsia is the sensation of epigastric discomfort. It may be a feature of potentially severe diseases such as peptic ulcer disease or gastric cancer. It may also be a symptom of *H. pylori* gastritis or NSAID gastritis.

Intermittent indigestion, heartburn or dyspepsia may be associated with:
» use of NSAIDs e.g. aspirin, ibuprofen, pain powders;
» spicy food, alcohol, carbonated drinks;
» smoking.

Complications that may develop in severe GORD are strictures, ulceration, Barrett's oesophagus and adenocarcinoma of the oesophagus. Two thirds of patients have a normal endoscopy which is termed non-erosive reflux disease (NERD) or non-ulcer dyspepsia (NUD) depending on the predominant symptom.

GENERAL MEASURES

LoE:IIIb[vi]

» Stop smoking.
» Limit alcohol intake.
» Eat small frequent meals.
» Avoid late night meals.
» Avoid fatty meals.
» Avoid carbonated beverages.
» Lose weight if overweight.
» Sleep with upper body elevated.
» Sleep on the left side.
» Avoid excessive exercise.
» Stop the use of potential ulcerogenic medicines, e.g. NSAIDs.
» If pale, check haemoglobin, and refer if anaemic.

All patients with alarm symptoms, i.e. weight loss, haematemesis or melaena, dysphagia, or anaemia, chest pain, or patients older than 60 years of age with new onset dyspepsia should have an endoscopy.

LoE:IVb[vii]

MEDICINE TREATMENT

New onset symptoms

Empiric therapy with a proton pump inhibitor (PPI) may be initiated **in the absence of alarm symptoms** (see referral section). Improvement of symptoms confirms acid-related disease.

- PPI, e.g.: LoE:I[viii]
- Pantoprazole, oral, 40 mg daily for 4 weeks. LoE:I[ix]
  - Ensure adherence to promote healing.

Recurrence of symptoms

After endoscopic confirmation of disease:

- PPI, e.g.:
- Pantoprazole, oral, 40 mg daily.
  - Decrease dose of PPI after 4 weeks, e.g.: pantoprazole, oral, 20 mg daily except for severe endoscopic GORD (Grade C or D LA classification) and Barret's oesophagus or specific advice from the endoscopist.

Barrett's oesophagus K22.7

- Restart PPI, e.g.:
- Pantoprazole, oral, 40 mg daily.

Note:
» Patients with Barrett's oesophagus usually need maintenance PPI therapy.
» There is no convincing evidence that long-term treatment of Barrett's oesophagus with PPIs reduces dysplasia or progression to malignancy.

REFERRAL
Discuss the following with a specialist:
» young patients who are PPI dependent and will require life-long therapy;
» patients unable to take PPIs;
» patients requiring high doses of PPIs;
» patients with large hiatus hernias and "volume reflux";
» a rolling hiatus hernia with obstructive symptoms – requires surgery;
» All patients with alarm symptoms:
  – Evidence of gastrointestinal bleeding,
  – Iron deficiency anaemia,
  – Anorexia,
  – Unexplained weight loss,
  – Dysphagia,
  – Odynophagia (painful swallowing),
  – Persistent vomiting, haematemesis, and/or melaena,
  – Gastrointestinal cancer in a first-degree relative.

1.1.4 HIATUS HERNIA
K44.0/K44.1/K44.9

GENERAL MEASURES
Manage GORD. See Section 1.1.3: Gastro-Oesophageal Reflux Disease (GORD) and dyspepsia.

1.1.5 INFLAMMATORY BOWEL DISEASE
K50.0-1/K50.8-9/K51.0-5/K51.8-9/K52.0-3/K52.8-9

DESCRIPTION
Inflammatory bowel disease is a chronic inflammatory disorder of the gastrointestinal tract that includes both Crohn's disease (CD) and ulcerative colitis. Abdominal pain, rectal bleeding, diarrhoea and weight loss characterise both CD and ulcerative colitis.

REFERRAL
Discuss all patients with a potential diagnosis of Crohn's disease or ulcerative colitis with a specialist.

1.1.6 PANCREATITIS, ACUTE

K85.0-3/K85.8-9

DESCRIPTION

Acute inflammatory condition of the pancreas.
Acute pancreatitis is based on the fulfilment of '2 out of 3' of the following criteria:

» clinical (upper abdominal pain),
» laboratory (serum amylase or lipase >3x upper limit of normal), and/or
» imaging (CT, MRI, ultrasonography) criteria.

Intense local inflammation results in pain, and local as well as systemic, complications. Disseminated intravascular coagulopathy (DIC), metabolic derangements and shock may occur.
Measurement of renal function and electrolytes measurements (including calcium) can be used to determine severity.

GENERAL MEASURES

» Parenteral fluid replacement to correct metabolic and electrolyte disturbances.
» Parenteral nutrition is associated with adverse outcomes and should only be considered in patients that cannot receive or tolerate nasogastric or enteral nutrition.
» Drainage of abscess/pseudocyst, if required.

MEDICINE TREATMENT

Pain:

- Morphine, IV, to a total maximum dose of 10 mg (see Appendix II, for individual dosing and monitoring for response and toxicity).

Acute symptomatic hypocalcaemia: E83.5

- Calcium gluconate 10%, IV infusion, 10 mL as a bolus over 10 minutes.
  - Follow with 60–120 mL diluted in 1 L sodium chloride 0.9%, administered over 12–24 hours. *LoE:III*
  - Monitor serum calcium at least 12 hourly.

If serum magnesium <0.5 mmol/L:

ADD

- Magnesium sulfate, IV infusion, 25–50 mmol in 12–24 hours.
  - 1 mL magnesium sulfate 50% = 2 mmol magnesium.

Antimicrobial therapy

Routine administration of prophylactic antibiotics is not necessary.

For infected necrosis of the pancreas:
Broad spectrum IV antibiotics: *LoE:III[x]*

- Amoxicillin/clavulanic acid, IV, 1.2 g 8 hourly for 10 days,

depending on clinical response. A

REFERRAL
Severe complications, e.g. necrosis; haemorrhagic or systemic complications; or infective pancreatitis.

1.1.7 PANCREATITIS, CHRONIC
K86.0-3/K86.8-9

DESCRIPTION
Chronic inflammatory condition of the pancreas with severe abdominal pain, which results in functional and structural damage. In most patients, this is a chronic, progressive disease that leads to exocrine and/or endocrine insufficiency.

GENERAL MEASURES
» Abstinence from alcohol reduces abdominal pain in the early stages of the disease.
» Stop smoking.
» Small frequent meals and restricted fat intake reduces pancreatic secretion and pain.
» When weight loss is not responding to exogenous enzymes and diet, consider supplementation with medium chain triglycerides.
» There is a risk of developing cancer of the pancreas. Consider this in patients who develop worsening pain, new onset diabetes or deterioration in exocrine function.
» Dietary advice by dietician.

MEDICINE TREATMENT
Treatment is aimed at:
» pain,
» exocrine dysfunction (malabsorption and diarrhoea),
» endocrine function. See Section 8.5.2: Type 1 Diabetes mellitus.

Analgesia
See Section 26.1: Pain, chronic.
Note: Pancreatic enzymes may reduce pain by negative feedback on pancreatic secretion.

Malabsorption
Supplementation of fat-soluble vitamins may be indicated.

- Pancreatic enzyme replacement e.g. Lipase, oral, equivalent to lipase 30 000 units per day, in divided doses with meals and/or snacks.
  - Titrate pancreatic enzyme replacement therapy until symptom control has been achieved.

REFFERAL

» Presence of pseudocyst for surgical intervention.
» Autoimmune chronic pancreatitis.

1.1.8 PEPTIC ULCER

K25.0-7/K25.9/K26.0-7/K26.9/K27.0-7/K27.9

DESCRIPTION

Ulcer in the stomach mucosa (gastric ulcer: GU) or first few centimetres of the duodenum (duodenal ulcer: DU), which penetrates into, or through the muscularis mucosa. Diagnosis is made after endoscopy as all GUs require biopsy to exclude malignancy.

GENERAL MEASURES

» Advise patient to avoid ulcerogenic medications, e.g. NSAIDs.
» Advise patient to stop smoking and drinking alcohol.
» Dietary advice by dietician.
» Patients with GUs and complicated DUs, those that have bled, perforated or are recurrent, must be rescoped at appropriate intervals until the ulcer has healed. *H. pylori* can be assessed at scope by rapid urease testing (RUT) or biopsy.

MEDICINE TREATMENT

***H. pylori* positive:**

The vast majority of GUs and DUs are associated with *H. pylori* infection and eradication therapy is indicated if infection is present. This will greatly reduce the rate of recurrent ulceration. Empiric eradication of *H. pylori* **is not recommended**.

H. pylori eradication: K25.0-7/K25.9/K26.0-7/K26.9/K27.0-7/K27.9 + (B98.0)

- Amoxicillin, oral, 1 g 12 hourly for 14 days. A — *LoE:Ib[xi]*

OR

For severe penicillin allergy: (Z88.0)

- Azithromycin, oral, 500 mg daily for 3 days. W

AND

- Metronidazole, oral, 400 mg 12 hourly for 14 days. A

Proton pump inhibitors (PPIs):

- PPI, e.g.:
- Pantoprazole, oral, 40 mg 12 hourly for 14 days.

Continue with PPI therapy as follows: — *LoE:IIIb[xii]*

- PPI, e.g.:
- Pantoprazole, oral, 40 mg daily.

- Duodenal ulcer: for up to 2 weeks.
- Gastric ulcer: for up to 6 weeks.

***H. pylori* negative:**

» These are usually a consequence of NSAID use.
» Stop NSAID until ulcer has healed.
» If patient is unable to stop NSAID, refer to specialist for guidance.

- PPI, e.g.:
- Pantoprazole, oral, 40 mg daily.
  - Duodenal ulcer: for up to 4 weeks.
  - Gastric ulcer: for up to 8 weeks.

LoE:IIIb[xiii]

Resistant disease

» Ulcer not healing.
» High-risk patients, i.e. poor surgical risk and the elderly or concomitant disease.

Maintenance therapy:

LoE:III[xiv]

- PPIs, e.g.:
- Pantoprazole, oral, 40 mg daily. Specialist initiated.

REFERRAL

» Failure of *H. pylori* eradication: Discuss with specialist.

1.2 HEPATIC DISORDERS

DESCRIPTION

Hepatitis (inflammation of the liver) may be infectious (caused by viral, bacterial, fungal, and parasitic organisms) or non-infectious (triggered by alcohol, drugs, autoimmune diseases, and metabolic diseases).

Causes of hepatitis includes idiosyncratic drug reactions, viral hepatitis (A, B, C, D, E), alcoholic hepatitis, non-alcoholic fatty liver disease, autoimmune hepatitis, Wilson's disease, ischaemic hepatopathy, Budd-Chiari syndrome, veno-occlusive disease, acute fatty liver of pregnancy/HELLP syndrome, malignant infiltration, partial hepatectomy, toxin exposure, including mushroom poisoning, sepsis, heat stroke or haemophagocytic lymphohistiocytosis.

1.2.1 HEPATITIS, NON-VIRAL

K70.1/K71.0-9/K73.0-2/K73.8-9/K75.4

* Notifiable medical condition if caused by agricultural chemicals or insecticides.

DESCRIPTION

Any form of hepatitis not caused by the common hepatotropic viruses.

Liver biopsy is indicated if hepatitis persists, or diagnosis is unclear.

GENERAL MEASURES

» Diet: If no hepatic encephalopathy, then normal protein intake is appropriate. With clinical monitoring of hepatic encephalopathy, maintain 1 to 1.5 g/kg daily protein intake.
» Avoid alcohol and other hepatotoxic agents.
» Monitor blood glucose regularly given potential risk of hypoglycaemia.

MEDICINE TREATMENT

If the patient is jaundiced with a prolonged INR (INR>2)

- Vitamin K1, IV, 10 mg
  - Administer as a slow IV injection.
  - Do not dilute or mix with other injectables.

LoE:IVb

If the patient is bleeding, give

LoE:IIb[xv]

- Lyophilised plasma, IV, 15mL/kg over 20-30 minutes.

OR

- Fresh Frozen Plasma, IV, 15mL/kg over 20-30 minutes.

AND

Discuss further management with a specialist.

Hepatitis due to infections

Antibiotic therapy based on culture, serology or suspected aetiology e.g. leptospirosis.

Alcohol-induced hepatitis

- Thiamine, oral, 300 mg daily.

Other vitamins if indicated.

Drug-induced hepatitis

Stop all potentially hepatotoxic medication immediately, in consultation with a specialist.

Auto-immune hepatitis K75.4

Patients with persistent hepatitis, negative viral markers and no hepatotoxins. Biopsy and/or various parameters are required to make the diagnosis.

<u>If autoimmune hepatitis:</u>

- Corticosteroids (intermediate-acting) e.g.:
- Prednisone, oral, 0.5 mg/kg daily.
  - Taper dose to a suitable maintenance dose. (Refer to Appendix II for an example of a dose reduction regimen.)

AND (in consultation with gastroenterologist or hepatologist)

- Azathioprine, oral, 0.5 mg/kg daily, titrated up to 1 mg/kg daily depending on response and WCC.

REFERRAL

» Where patients cannot be managed locally or biopsy cannot be done, i.e. diagnosis is unclear.
» Non-resolving hepatitis.

Note: Refer timeously before extensive liver damage occurs.

1.2.2 LIVER FAILURE, ACUTE

K72.0/K72.9

DESCRIPTION

Acute liver failure refers to the development of severe acute liver injury with encephalopathy and impaired synthetic function (INR of ≥1.5) in a patient without cirrhosis or pre-existing liver disease. There are many causes, but the commonest are viral hepatitis, alcohol, drug-induced liver injury, toxins or ischaemic hepatitis.

GENERAL MEASURES

» Patient education.
» Avoid hepatotoxic drugs and alcohol.
» Rest and reduce physical activity.
» Protein restriction is indicated for encephalopathy; however, severe protein restriction may accentuate catabolism. Use increments of 20 g protein per day, aiming for 1 g/kg/day as tolerated.
» Monitor blood glucose regularly because hypoglycaemia is common.
» Correct electrolyte disturbances.
» Exclude GI bleed and infection.
» Avoid factors (especially medications) that may worsen or precipitate functional deterioration.
» Avoid vigorous paracentesis.
» If the patient is bleeding, check INR and correct coagulopathy with FFP or lyophilised plasma.

MEDICINE TREATMENT

- Lactulose, oral, 10–30 mL 8 hourly, titrated to attain 2–3 soft stools per day.

Note: Do not give antibiotics unless there is evidence of bacterial sepsis.

REFERRAL

» All cases of severe acute liver failure should be discussed with a specialist.

1.2.3 PORTAL HYPERTENSION AND CIRRHOSIS

R18/K72.9/K74.6+(I98.2*/I98.3*)

DESCRIPTION

The complications of portal hypertension include:

» variceal bleeds,
» ascites,
» hepatic encephalopathy (HE),
» splenomegaly with hypersplenism,
» hepatorenal syndrome,
» hepato-pulmonary syndrome or porto-pulmonary hypertension.

GENERAL MEASURES

» Ascites: Perform diagnostic paracentesis if indicated. Restrict sodium intake, i.e. ≤ 2 g/day or ≤ 88 mmol/day.
» Monitor weight regularly.
» Encephalopathy: with acute HE, protein restrict (ideally under advice of dietician), otherwise 1–1.5 g/kg protein per day.
» Exclude infection, high protein load, occult bleed, sedatives, electrolyte disturbances and hepatocellular carcinoma.
» Variceal bleeding: endoscopic variceal ligation and/or immediate referral for advanced management.

MEDICINE TREATMENT

Ascites R18

- Spironolactone, oral, 100 mg daily.
  AND
- Furosemide, oral, 40 mg daily.

For spironolactone and furosemide:

- Increase spironolactone and furosemide dose by 100 mg and 40 mg, respectively, every 3–5 days, to a maximum dose of 400 mg spironolactone and 160 mg of furosemide depending on serum Na^+, K^+, urea and creatinine.
- Spironolactone may cause hyperkalaemia.
- Rapid fluid shifts may precipitate acute liver and/or renal failure.

Monitoring of sodium, potassium and renal function is essential in patients taking spironolactone. Avoid spironolactone if eGFR <30 mL/minute.

LoE:III[xvi]

Measure response to diuretics by weighing patient daily. Aim for maximal weight loss of:

» Patients without oedema: 500 g/day
» Patients with oedema: 1 000 g/day

Tense ascites R18
Albumin replacement must be given if ≥5 L of fluid is drained by paracentesis, or if there is pre-existing renal dysfunction:

- Albumin, IV, 40 g (20%), as an infusion. LoE:II[xvii]
  - Refer to specialist unit to consider transjugular intrahepatic portosystemic (TIP) shunt or potential transplant.
- Introduce diuretics and titrate doses as necessary to prevent recurrence of ascites (see above).

Note:
» Avoid NSAIDS and ACE-inhibitors.
» Exclude spontaneous bacterial peritonitis in patients with new onset ascites.

Refractory ascites R18
Defined as:
» No response to optimal diuretic therapy despite sufficient sodium restriction (≤2 g/day or ≤88 mmol/day) and avoidance of NSAIDs.
» Ascites that recurs rapidly following therapeutic paracentesis.

Perform serial large volume paracentesis, as an outpatient, usually not more frequently than every 2 weeks.
Haemodynamic collapse is more likely in patients who have intravascular volume depletion. Check renal function before paracentesis.

Albumin replacement must be given if ≥5 L of fluid is removed by paracentesis:

- Albumin, IV, 40 g (20%), as an infusion. LoE:II[xviii]

Encephalopathy

- Lactulose, oral, 10–30 mL 8 hourly, depending on stool number and consistency (aim for 2 soft stools/day).

Look for precipitating factors: Sepsis, protein load, GIT bleed, over diuresis, sedation.

Oesophageal varices I85.0/I85.9
To reduce the risk of bleeding:

- Beta-blocker, e.g.: LoE:III[xix]
- Propranolol, oral, 20–40 mg 12 hourly. Titrate to resting pulse rate of 50–60 beats per minute. Monitor pulse and BP.

REFERRAL

Refer to specialist unit to consider TIP shunt, endoscopic variceal ligation or potential transplant.

1.2.4 HEPATITIS, VIRAL

*Notifiable medical condition.

DESCRIPTION

Hepatitis caused by one of the hepatotropic viruses, hepatitis A, B, C, D and E.

1.2.4.1 HEPATITIS B, ACUTE

B16.0-2/B16.9

GENERAL MEASURES

» Bed-rest until acute phase has resolved.
» Avoid alcohol during the illness and for ≥ 6 months after clinical recovery.
» Screen sexual contacts of patients with acute hepatitis B. Non-immune contacts (negative for hepatitis B surface antibodies) should receive hepatitis B active immunisation (see Section 9.2: Adult vaccination).

MEDICINE TREATMENT

For nausea and vomiting: (R11)

- Metoclopramide, IV/oral, 10 mg 8 hourly as required.

Hepatitis B virus: prophylaxis following exposure e.g. needle stick injury
S61.0 + (W46.22+Z20.5+Z29.8)

» Persons at risk can be protected by passive immunisation with hyper immune serum globulin prepared from blood containing anti-HBs.
» It is essential that all categories of healthcare workers (HCW) at risk of contact with bodily fluids, including cleaning staff and home-based or family caregivers, are screened and fully vaccinated against hepatitis B if nonimmune.
» All occupational exposure incidents must be adequately documented for possible subsequent compensation.
» Recommended post-exposure management for HCW exposed to infectious material from patients with infectious hepatitis B (either surface antigen or e antigen positive).

Check vaccination status and antibody response of HCW (See table below for management depending on immunity):

Vaccination status and antibody response status of HCW	Source patient status & treatment		
	HBsAg positive	**HBsAg negative**	**HBsAg unknown**
Unvaccinated **OR** vaccination incomplete	• HBIG, IM, 500 units* • Hep B vaccine (3 doses at monthly intervals)	• Initiate Hep B vaccination (month 0, 1 and 6)	• HBIG, IM, 500 units* • Hep B vaccine (3 doses at monthly intervals)
Vaccinated **AND** HBsAb ≥10 units/mL[#]	No treatment	No treatment	No treatment
Vaccinated **AND** HBsAb <10 units/mL	• HBIG, IM, 500 units* • Repeat Hep B vaccine (3 doses at monthly intervals)	• Initiate Hep B vaccination (month 0, 1 and 6)	• HBIG, IM, 500 units* • Repeat Hep B vaccine (3 doses at monthly intervals)

* HBIG and first dose of vaccine to be given simultaneously, but at different sites.
[#] If the delay in obtaining HBsAb results is more than 24 hours initiate treatment as for vaccinated AND HBsAb <10 units/mL.
Table 1.1: Prophylaxis following Hepatitis B exposure

1.2.4.2 HEPATITIS B, CHRONIC (NON-HIV COINFECTION)

B18.0-2/B18.8-9

Consult the most recent Hepatitis Guidelines from the National Department of Health for comprehensive monitoring recommendations.

DESCRIPTION

» HBV is most commonly transmitted horizontally in children <5 years of age. Vertical mother to child transmission and adult transmission, sexually or through a parenteral route, can also occur.
» Acute infection may be asymptomatic or present as acute hepatitis.
» A proportion of patients develop chronic hepatitis (defined as abnormalities listed in the table below persisting for >6 months), which can result in cirrhosis and hepatocellular carcinoma.
» It is essential to know the HIV status of all patients with chronic hepatitis B before considering therapy.
» Antiviral therapy is not indicated for acute hepatitis B infection.

There are 5 potential phases of chronic hepatitis B infection which determine the need for treatment:

Phase	Serology	Viral load (HBV DNA) IU/mL	ALT	Management LoE:III[xx]
1. HBeAg-positive chronic HBV infection *Immune Tolerant*	» HBsAg positive » HBeAg positive	>20 000 (usually >200 000)	Normal	» Treatment not routinely needed but should be followed up. » Treat only if on immunosuppressive therapy to prevent hepatitis B flares.
2. HBeAg-positive chronic hepatitis B *Immune clearance*	» HBsAg positive » HBeAg positive	>20 000	Elevated	» Treatment required.
3. HBeAg-negative chronic HBV infection *Immune Control*	» HBsAg positive » HBeAg negative	<2 000	Normal	» Treatment not routinely needed but should be followed up. » Treat only if on immunosuppressive therapy to prevent hepatitis B flares.
4. HBeAg-negative chronic hepatitis B *Immune Escape*	» HBsAg positive » HBeAg negative	>2 000	Elevated	» Treatment required.
5. Occult hepatitis B	» HBsAg negative » HBsAb negative » HB IgG core Ab positive	<200	-	» No follow-up required. » Treat only if on immunosuppressive therapy to prevent hepatitis B flares.

HBsAg: hepatitis B surface antigen; *HBsAb:* hepatitis B surface antibody; *HBIG:* hepatitis B immunoglobulin

Table 1.2: Phases of Chronic Hepatitis B infection

Treat all patients with cirrhosis regardless of ALT level, HBeAg status and HBV viral load, to prevent hepatitis B flares that will lead to decompensation. Screen all categories of healthcare workers (HCW) at risk of contact with bodily fluids, including cleaning staff, home-based or family caregivers and vaccinate against hepatitis B if not immune (see Section 24.1.5: Management of close contacts of patients with hepatocellular carcinoma).

MEDICINE TREATMENT

<u>If eGFR > 50mL/min:</u>

- Tenofovir disoproxil fumarate (TDF), oral, 300 mg daily.

LoE:III[xxi]

<u>If eGFR 15-50mL/min (or on haemodialysis):</u>

- Tenofovir alafenamide (TAF), oral, 25 mg daily.

Aims of treatment LoE:IIb[xxii]

HBeAg-positive disease:

» Sustained HBsAg loss off therapy, with/without the development of anti-HBs, **and**
» Suppression of HBV DNA to undetectable or low (<2000 IU/mL) levels, **and**
» Normalisation of ALT, **and**
» Sustained HBeAg loss and seroconversion to anti-HBe.

HBeAg-negative disease:

» Sustained HBsAg loss off therapy, with/without the development of anti-HBs, **and**
» Suppression of HBV DNA to undetectable or low (<2000 IU/mL), **and**
» Normalisation of ALT.

Monitoring whilst on tenofovir

Monitoring test	When to perform test
Serum phosphate and urine protein	Baseline
INR	Baseline, Week 4
Serum creatinine	All patients: Baseline Patients on TDF: Month 3, month 10, and every 12 months thereafter.
ALT	Baseline, Week 4, and every 12 weeks thereafter.
FBC+Diff	Baseline, Week 4, and every 12 weeks thereafter
HBeAg and Anti-HBe	HBeAg-positive patients: Every 12 months
HBsAg	HBeAg-positive patients: HBsAg every 6 months after anti-HBe seroconversion HBeAg-negative patients: HBsAg every 6 months with persistently undetectable HBV DNA
HBV DNA levels	HBeAg-positive patients: 12 months after HBeAg seroconversion

Table 1.3: Monitoring tests whilst on tenofovir

Adapted from: National Department of Health, National guidelines for the management of viral hepatitis, 2019. Available at www.health.gov.za

Duration of tenofovir treatment:

» HBeAg-positive patients: discontinue 12 months after HBeAg seroconversion and in association with persistently normal ALT levels and undetectable HBV DNA levels.
» HBeAg-negative patients: Long-term therapy unless HBsAg seroconversion is achieved.
» Cirrhotic patients: Lifelong treatment.

REFERRAL
Failure of, or contraindications to, tenofovir disoproxil fumarate and tenofovir alafenamide.

1.2.4.3 HEPATITIS B, CHRONIC (HIV CO-INFECTION)
See chapter 10: HIV and AIDS.

1.2.4.4 HEPATITIS C, CHRONIC
Consult a specialist.

1.2.5 LIVER ABSCESS, PYOGENIC
K75.0

DESCRIPTION
Focal bacterial infection, usually polymicrobial, of the liver with pus. Multiple abscesses are not uncommon.

GENERAL MEASURES
Drainage is essential in all cases. This should preferably be done percutaneously by inserting a catheter under ultrasound guidance.

MEDICINE TREATMENT
Empiric antibiotic therapy

- Amoxicillin/clavulanic acid, oral, 875/125 mg 12 hourly. A

If unable to tolerate oral therapy:

- Amoxicillin/clavulanic acid, IV, 1.2 g 8 hourly. A

Duration of antibiotic therapy is ill defined but may need to be for as long as 12 weeks in cases of multiple abscesses. Continue until drainage is complete and CRP has returned to normal values. Monitoring response to therapy by ultrasound is not useful due to slow resolution of abscesses on imaging.

1.2.6 LIVER ABSCESS, AMOEBIC
A06.4

DESCRIPTION
Focal hepatic infection due to *E. histolytica*. Only about a third of cases have concomitant amoebic colitis. Diagnosis can be excluded if the serological test is negative. It is essential to exclude pyogenic infection (a diagnostic aspirate should be taken under ultrasound guidance in all cases where there is doubt).

GENERAL MEASURES

Drainage is recommended for abscesses that are large (i.e. >10 cm diameter), involve the left lobe, or are near the surface of the liver. Drainage can be achieved by percutaneous aspiration under ultrasound guidance.

MEDICINE TREATMENT

- Metronidazole, oral, 800 mg 8 hourly for 10 days. A

LoE:III[xxiii]

1.2.7 CHOLECYSTITIS, ACUTE AND CHOLANGITIS, ACUTE

K81.0/K83.0

GENERAL MEASURES

Surgical drainage/cholecystectomy according to indication and/or patient's condition.

MEDICINE TREATMENT

Acute cholecystitis

Mild and asymptomatic cases without risk factors may not require antibiotic treatment. If signs of infection present and/or risk factors for severe disease are present, such as:

» Elderly patients (>60 years of age).
» Co-morbid conditions.
» Immune compromised.

Acute cholecystitis and acute cholangitis

- Amoxicillin/clavulanic acid, oral, 875/125 mg 12 hourly. A

If unable to tolerate oral therapy:

- Amoxicillin/clavulanic acid, IV, 1.2 g 8 hourly. A

REFERRAL

» Clinical deterioration or failure to improve.
» Fistulae or perforation.
» Need for complicated surgery.

1.3 DIARRHOEA

1.3.1 CHOLERA

A00.0-1/A00.9

*Notifiable medical condition.

DESCRIPTION

Diarrhoea due to *Vibrio cholerae*, often in outbreaks.

GENERAL MEASURES

Rehydration is the cornerstone of management. Oral rehydration is preferred.

MEDICINE TREATMENT

- Oral rehydration solution (ORS) by mouth or nasogastric tube.
  - If enteral administration not possible, e.g., patient is vomiting, profoundly dehydrated, or stuporous:

IV treatment if unable to tolerate oral rehydration: *LoE:IVb*[xxiv]

- Ringers lactate, IV (preferred).

OR

- Sodium chloride, 0.9%, IV.

AND

Antibiotic therapy: *LoE:III*[xxv]

- Ciprofloxacin, oral, 1 g as a single dose.
  - Adjust antibiotic choice, according to the sensitivity of the isolate responsible for the local epidemic.

CAUTION

Dextrose 5% should not be used for fluid replacement in patients with cholera as it does not contain electrolytes, which are required to ensure adequate fluid resuscitation.

1.3.2 DYSENTERY (ACUTE INFLAMMATORY DIARRHOEA)

A02.0/A02.9/A03.0-3/A03.8-9/A04.2/A04.5/A04.8-9

DESCRIPTION

Diarrhoea with neutrophils, blood and/or mucus.

GENERAL MEASURES

» Rehydration is the cornerstone of management. This should be done with oral rehydration solution (ORS) unless the patient is vomiting or profoundly dehydrated.
» Perform a stool culture.

MEDICINE TREATMENT

CAUTION
Loperamide is contraindicated as it may result in toxic megacolon.

Antibiotic therapy
Consider in patients with signs of sepsis, severe cases, or significant underlying disease:

- Ceftriaxone, IV 1 g daily. W

Switch antibiotic when clinically appropriate:

- Ciprofloxacin, oral, 500 mg 12 hourly, ideally based on culture and sensitivity if available. W

For uncomplicated dysentery in patients with no co-morbidity:

- Ciprofloxacin, oral, 500 mg 12 hourly for 3 days. W
  - Extend treatment duration to 7 days in patients with significant co-morbidity, e.g. immunocompromised patients.

REFERRAL
Persistent diarrhoea with blood and mucus for longer than 2 weeks.

1.3.3 DIARRHOEA, ACUTE NON-INFLAMMATORY
A04.1

DESCRIPTION
Diarrhoea without macroscopic blood or mucus, or neutrophils on microscopy. Common causes include viruses and enterotoxigenic strains of *E. coli*.
Note: Neutropenic patients may have inflammatory diarrhoea in the absence of neutrophils.

GENERAL MEASURES
Rehydration is the cornerstone of management. This should be done with oral rehydration solution (ORS) unless the patient is vomiting or profoundly dehydrated.

MEDICINE TREATMENT
- Loperamide, oral, 4 mg immediately, followed by 2 mg after each loose stool. *LoE:III*[xxvi]
  - Maximum dose: refer to dose table below

Weight band	Maximum daily dose (equivalent maximum number of 2 mg tablets per day)
34-39 kg	10 mg (5 tablets)
40-46 kg	12 mg (6 tablets)
47-53 kg	14 mg (7 tablets)
≥ 54 kg	16 mg (8 tablets)

1.3.4 CLOSTRIDUM DIFFICILE (*CLOSTRIDIOIDES DIFFICILE*) DIARRHOEA

A04.7

*Notifiable medical condition.

DESCRIPTION

» Diarrhoea caused by altered bowel flora due to antibiotic exposure.
» *Clostridium difficile* (*Clostridioides difficile*) infection may result in severe disease and/or the development of pseudomembranous colitis.
» Diagnosis is confirmed in the laboratory on a stool sample. Patients with unexplained and new-onset diarrhoea of more than 3 unformed stools in 24 hours should be tested. Repeat testing (within 7 days) is not recommended.

GENERAL MEASURES

» The most important aspect of management is discontinuation of antibiotics.
» Rehydration may be necessary. This should be done with oral rehydration solution (ORS) unless the patient is vomiting or profoundly dehydrated.
» Patients with known or suspected *Clostridium difficile* infection should be placed on contact precaution according to institutional infection control and prevention measures.
» Contact precautions should be maintained for at least 48 hours after diarrhoea has resolved.
» Healthcare workers and all close contacts should perform regular handwashing with soap and water. Alcohol-based hand sanitizer does not kill spores.

MEDICINE TREATMENT

CAUTION
Loperamide is contraindicated as it may result in toxic megacolon.

Mild to moderate infection
Laboratory results confirm toxigenic *Clostridium difficile* infection, but diarrhoea does not settle on antibiotic withdrawal:

- Metronidazole, oral, 400 mg 8 hourly for 10 days. A

Severe infection
Laboratory results confirm toxigenic *Clostridium difficile* infection, WCC >15 x10^9/L or serum creatinine >132 micromol/L, or other risk predictors of severity (immunodeficiency, intensive care admission, serious comorbidity, age >65 years of age).

- Vancomycin, oral, 125 mg 6 hourly (give parenteral formulation orally) for 10 days. W

Fulminant infection

If ileus or toxic megacolon or hypotension/shock:

- Vancomycin, oral, 125 mg 6 hourly (give parenteral formulation orally) for 10 days. W

AND

- Metronidazole, IV, 500 mg 8 hourly for 10 days. A

Switch to oral metronidazole, if/when possible, to complete 10-day course.

Recurrence

If metronidazole was used during the first episode:

- Vancomycin, oral, 125 mg 6 hourly (give parenteral formulation orally) for 10 days. W

If vancomycin was used during the first episode, administer oral vancomycin as a tapered and pulsed regimen:

- Vancomycin, oral, 125 mg (give parenteral formulation orally) as follows: W
  - 6 hourly for 10 days, then
  - 12 hourly for 7 days, then
  - once daily for 7 days, then
  - every 2nd or 3rd day for 2 to 8 weeks.

LoE:I[xxvii]

REFERRAL

» Surgical consult should be obtained in all patients with complicated *Clostridium difficile* infection (e.g. bowel perforation, hypotension requiring vasopressor therapy, clinical signs of sepsis).
» Failure to improve on medical therapy after 5 days.

1.3.5 AMOEBIC DYSENTERY

A06.0-1

DESCRIPTION

Diarrhoea with blood and/or mucus due to *E. histolytica*. Organism must be demonstrated on a warm stool specimen with microscopy.

GENERAL MEASURES

» Rehydration may be necessary. This should be done with oral rehydration solution (ORS) unless the patient is vomiting or profoundly dehydrated.
» Surgery for bowel perforation.

MEDICINE TREATMENT

LoE:III[xxviii]

- Metronidazole, oral, 800 mg 8 hourly for 10 days. A

CAUTION
Loperamide is contraindicated as it may result in toxic megacolon.

1.3.6 GIARDIASIS
A07.1

DESCRIPTION
Infection with the protozoan parasite, *G. lamblia* which colonises the proximal small intestine. Does not typically present with acute diarrhoea.

GENERAL MEASURES
Fluid and electrolyte replacement in severe diarrhoea.

MEDICINE TREATMENT
- Metronidazole, oral, 2 g daily for 3 days. A

1.3.7 TYPHOID
See Section 9.11: Typhoid fever.

1.3.8 BACTERIAL PERITONITIS
K65.0/K65.8-9

DESCRIPTION
Infection of the peritoneum, usually secondary to a surgical cause such as perforated bowel. In this setting polymicrobial infection with anaerobes, Gram-positive cocci, and Enterobacteriaceae are usually found. Primary or spontaneous bacterial peritonitis is much less common and usually complicates ascites in patients with portal hypertension. This is not usually polymicrobial but due generally to Enterobacteriaceae such as *E. coli*. Spontaneous bacterial peritonitis is often culture-negative but is diagnosed by ascitic neutrophil count >0.25 x 10^9/L (250 cells/mm^3).

GENERAL MEASURES
Secondary peritonitis
» Intravenous fluids and nasogastric suction.
» Prompt surgical intervention is essential.

MEDICINE TREATMENT
Empiric antibiotic therapy
For surgical causes of peritonitis:
- Amoxicillin/clavulanic acid, IV, 1.2 g 8 hourly. A

As soon as patient can tolerate oral medication:
- Amoxicillin/clavulanic acid, oral, 875/125 mg 12 hourly. A

For spontaneous bacterial peritonitis:
- Ceftriaxone, IV, 1 g daily. W
  - Patients not responding to ceftriaxone after 48 hours, consult a specialist.

Switch to oral therapy when clinically appropriate according to culture or treat with:

- Ciprofloxacin, oral, 500 mg 12 hourly. W
  - Total duration of therapy: 14 days.

References:

[i] Hassan C et al. Bowel preparation for colonoscopy: European Society for Gastrointestinal Endoscopy (ESGE)[i] guidelines: update 2019. DOI https://doi.org/10.1055/a-0959-0505. Published online: 2019 | Endoscopy

[ii] Polyethylene glycol, oral: Park DI, Park SH, Lee SK, Baek YH, Han DS, Eun CS, Kim WH, Byeon JS, Yang SK. Efficacy of prepackaged, low residual test meals with 4L polyethylene glycol versus a clear liquid diet with 4L polyethylene glycol bowel preparation: a randomized trial. J GastroenterolHepatol. 2009 Jun;24(6):988-91. http://www.ncbi.nlm.nih.gov/pubmed/25053529

Sodium sulfate, oral: Johnson DA, Barkun AN, Cohen LB, Dominitz JA, Kaltenbach T, Martel M, Robertson DJ, Boland CR, Giardello FM, Lieberman DA, Levin TR, Rex DK. Optimizing adequacy of bowel cleansing for colonoscopy: recommendations from the U.S. multi-society task force on colorectal cancer. GastrointestEndosc. 2014 Oct;80(4):543-62. http://www.ncbi.nlm.nih.gov/pubmed/25220509

Sodium sulfate, oral: Di Palma JA, Rodriguez R, McGowan J, Cleveland M. A randomized clinical study evaluating the safety and efficacy of a new, reduced-volume, oral sulfate colon-cleansing preparation for colonoscopy. Am J Gastroenterol 2009;104:2275-84. http://www.ncbi.nlm.nih.gov/pubmed/19584830

Sodium sulfate, oral: Rex DK, Di Palma JA, Rodriguez R, McGowan J, Cleveland M. A randomized clinical study comparing reduced-volume oral sulfate solution with standard 4- liter sulfate-free electrolyte lavage solution as preparation for colonoscopy. GastrointestEndosc 2010;72:328-36. http://www.ncbi.nlm.nih.gov/pubmed/20646695

[iii] Polyethylene glycol, oral/ sodium sulfate, oral (split dosing): Bucci C, Rotondano G, Hassan C, Rea M, Bianco MA, Cipolletta L, Ciacci C, Marmo R. Optimal bowel cleansing for colonoscopy: split the dose! A series of meta-analyses of controlled studies. GastrointestEndosc. 2014 Oct;80(4):566-576.e2. http://www.ncbi.nlm.nih.gov/pubmed/25053529

[iv] Adjunctive agents: American Society of Colon and Rectal Surgeons (ASCRS); American Society for Gastrointestinal Endoscopy (ASGE); Society of American Gastrointestinal and Endoscopic Surgeons (SAGES), Wexner SD, Beck DE, Baron TH, Fanelli RD, Hyman N, Shen B, Wasco KE. A consensus document on bowel preparation before colonoscopy: prepared by a task force from the American Society of Colon and Rectal Surgeons(ASCRS), the American Society for Gastrointestinal Endoscopy (ASGE), and the Society of American Gastrointestinal and Endoscopic Surgeons (SAGES). SurgEndosc. 2006 Jul;20(7):1147-60. http://www.ncbi.nlm.nih.gov/pubmed/16763922

Adjunctive agents: Rhodes JB, Engstrom J, Stone KE. Metoclopramide reduces the distress associated with colon cleansing by an oral electrolyte overload. GastrointestEndosc 1978;24:162-3.http://www.ncbi.nlm.nih.gov/pubmed/348558

Adjunctive agents: Brady CE III, DiPalma JA, Pierson WP. Golytely lavage: is metoclopramide necessary? Am J Gastroenterol 1985;80:180-4.http://www.ncbi.nlm.nih.gov/pubmed/3976636

Adjunctive agents: Brady CE 3rd, DiPalma JA, Beck DE. Effect of bisacodyl on gut lavage cleansing for colonoscopy. Am Clin Res 1987;19:34-8. http://www.ncbi.nlm.nih.gov/pubmed/3555277

[v] Amoxicillin/clavulanic acid, oral/IV (severe disease): South African Antibiotic Stewardship Programme. A Pocket Guide to Antibiotic Prescribing for Adults in South Africa, 2015. http://www.fidssa.co.za/Content/Documents/SAASP_Antibiotic_Guidelines_2015.pdf

[vi] Moayyedi PM, Lacy BE, Andrews CN, et al. ACG and CAG clinical guideline: Management of dyspepsia. Am J Gastroenterol. 2017 Jul;112(7):988-1013. http://doi. org/10.1038/ajg.2017.154

Cheddie S et al. Age is a predictor of significant endoscopic findings in dyspepsia patients in South Africa. Southern African Journal of Surgery 2020; 58(1):14-17 http://dx.doi.org/10.17159/2078-5151/2020/v58n1a2814.

[viii] Proton pump inhibitor, oral: Sigterman KE, van Pinxteren B, Bonis PA, Lau J, Numans ME. Short-term treatment with proton pump inhibitors, H2-receptor antagonists and prokinetics for gastro-oesophageal reflux disease-like symptoms and endoscopy negative reflux disease. Cochrane Database Syst Rev. 2013 May 31;5:CD002095. http://www.ncbi.nlm.nih.gov/pubmed/23728637

Proton pump inhibitor, oral (therapeutic class): National Department of Health: Affordable Medicines, EDP-Adult Hospital level. Medicine Review: PPIs, therapeutic class review, April, 2018. http://www.health.gov.za/

[ix] Proton pump inhibitor, oral (duration of 4 weeks): McDonagh MS, Carson S, Thakurta S. Drug Class Review: Proton Pump Inhibitors: Final Report Update 5 [Internet]. Portland (OR): Oregon Health & Science University; 2009 May. Available from http://www.ncbi.nlm.nih.gov/books/NBK47260/

[x] Amoxicillin/clavulanic acid, IV (abscess of the pancreas): South African Antibiotic Stewardship Programme. A Pocket Guide to Antibiotic Prescribing for Adults in South Africa, 2015. http://www.fidssa.co.za/Content/Documents/SAASP_Antibiotic_Guidelines_2015.pdf

[xi] NDoH evidence review. H.pylori eradication. 4 June 2020.

Azithromycin: Dong J, Yu XF, Zou J. Azithromycin-containing versus standard triple therapy for Helicobacter pylori eradication: a meta-analysis. World J Gastroenterol. 2009 Dec 28;15(48):6102-10. http://www.ncbi.nlm.nih.gov/pubmed/20027685

Azithromycin: National Department of Health. Essential Drugs Programme. Medicine review: The efficacy of Azithromycin compared to Clarithromycin in the treatment of *H.Pylori* infection, 26 November 2015. http://health.gov.za/

[xii] Proton pump inhibitor, oral (*H.pylori* +ve): Leontiadis GI, Sharma VK, Howden CW. Proton pump inhibitor therapy for peptic ulcer bleeding: Cochrane collaboration meta-analysis of randomized controlled trials. Mayo Clin Proc. 2007 Mar;82(3):286-96. http://www.ncbi.nlm.nih.gov/pubmed/17352364

Proton pump inhibitor, oral (*H.pylori* +ve): Neumann I, Letelier LM, Rada G, Claro JC, Martin J, Howden CW, Yuan Y, Leontiadis GI. Comparison of different regimens of proton pump inhibitors for acute peptic ulcer bleeding.

Cochrane Database Syst Rev. 2013 Jun 12;6:CD007999. http://www.ncbi.nlm.nih.gov/pubmed/23760821

Proton pump inhibitor, oral (*H.pylori* +ve): South African Medicines Formulary. 12th Edition. Division of Clinical Pharmacology. University of Cape Town, 2016.

Proton pump inhibitor, oral (therapeutic class): National Department of Health: Affordable Medicines, EDP-Adult Hospital level. Medicine Review: PPIs, therapeutic class review, April, 2018. http://www.health.gov.za/

Proton pump inhibitor, oral (therapeutic class): McDonagh MS, Carson S, Thakurta S. Drug Class Review: Proton Pump Inhibitors: Final Report Update 5 [Internet]. Portland (OR): Oregon Health & Science University; 2009 May. Available from http://www.ncbi.nlm.nih.gov/books/NBK47260/

Proton pump inhibitor, oral (therapeutic class): National Institute for Health and Care Excellence: Clinical Guidelines: Gastro-oesophageal reflux disease and dyspepsia in adults: investigation and management. https://www.nice.org.uk/guidance/cg184

[xiii]Proton pump inhibitor, oral (therapeutic class): National Department of Health: Affordable Medicines, EDP-Adult Hospital level. Medicine Review: PPIs, therapeutic class review, April, 2018. http://www.health.gov.za/

Proton pump inhibitor, oral (therapeutic class): McDonagh MS, Carson S, Thakurta S. Drug Class Review: Proton Pump Inhibitors: Final Report Update 5 [Internet]. Portland (OR): Oregon Health & Science University; 2009 May. Available from http://www.ncbi.nlm.nih.gov/books/NBK47260/

Proton pump inhibitor, oral (therapeutic class): National Institute for Health and Care Excellence: Clinical Guidelines: Gastro-oesophageal reflux disease and dyspepsia in adults: investigation and management. https://www.nice.org.uk/guidance/cg184

[xiv]Proton pump inhibitor, oral (therapeutic class): National Department of Health: Affordable Medicines, EDP-Adult Hospital level. Medicine Review: PPIs, therapeutic class review, April, 2018. http://www.health.gov.za/

Proton pump inhibitor, oral (therapeutic class): McDonagh MS, Carson S, Thakurta S. Drug Class Review: Proton Pump Inhibitors: Final Report Update 5 [Internet]. Portland (OR): Oregon Health & Science University; 2009 May. Available from http://www.ncbi.nlm.nih.gov/books/NBK47260/

Proton pump inhibitor, oral (therapeutic class): National Institute for Health and Care Excellence: Clinical Guidelines: Gastro-oesophageal reflux disease and dyspepsia in adults: investigation and management. https://www.nice.org.uk/guidance/cg184

[xv] Fresh frozen plasma/ Lyophilised plasma: Williamson LM, Llewelyn CA, Fisher NC, Allain JP, Bellamy MC, Baglin TP, Freeman J, Klinck JR, Ala FA, Smith N, Neuberger J, Wreghitt TG. A randomized trial of solvent/detergent-treated and standard fresh-frozen plasma in the coagulopathy of liver disease and liver transplantation. Transfusion. 1999 Nov-Dec;39(11-12):1227-34. http://www.ncbi.nlm.nih.gov/pubmed/10604250

[xvi] Spironolactone: Runyon BA; AASLD Practice Guidelines Committee. Management of adult patients with ascites due to cirrhosis: an update. Hepatology. 2009 Jun;49(6):2087-107.http://www.ncbi.nlm.nih.gov/pubmed/19475696

Spironolactone: South African Medicines Formulary. 12th Edition. Division of Clinical Pharmacology. University of Cape Town, 2016.

Furosemide:Runyon BA; AASLD Practice Guidelines Committee. Management of adult patients with ascites due to cirrhosis: an update. Hepatology. 2009 Jun;49(6):2087-107. http://www.ncbi.nlm.nih.gov/pubmed/19475696

[xvii] Albumin, IV: AASLD Practice Guidelines Committee. Management of adult patients with ascites due to cirrhosis: an update. Hepatology. 2009 Jun;49(6):2087-107. http://www.ncbi.nlm.nih.gov/pubmed/19475696

Albumin, IV: Bernardi M, Caraceni P, Navickis RJ, Wilkes MM. Albumin infusion in patients undergoing large-volume paracentesis: a meta-analysis of randomized trials. Hepatology. 2012 Apr;55(4):1172-81. http://www.ncbi.nlm.nih.gov/pubmed/22095893

[xviii] Albumin, IV: AASLD Practice Guidelines Committee. Management of adult patients with ascites due to cirrhosis: an update. Hepatology. 2009 Jun;49(6):2087-107. http://www.ncbi.nlm.nih.gov/pubmed/19475696

Albumin, IV: Bernardi M, Caraceni P, Navickis RJ, Wilkes MM. Albumin infusion in patients undergoing large-volume paracentesis: a meta-analysis of randomized trials. Hepatology. 2012 Apr;55(4):1172-81. http://www.ncbi.nlm.nih.gov/pubmed/22095893

[xix] Propranolol, oral: Garcia-Tsao G, Abraldes JG, Berzigotti A, Bosch J. Portal hypertensive bleeding in cirrhosis: Risk stratification, diagnosis, and management: 2016 practice guidance by the American Association for the study of liver diseases. Hepatology. 2017 Jan;65(1):310-335. https://www.ncbi.nlm.nih.gov/pubmed/27786365

Propranolol, oral: Tripathi D, Stanley AJ, Hayes PC, Patch D, Millson C, Mehrzad H, Austin A, Ferguson JW, Olliff SP, Hudson M, Christie JM; Clinical Services and Standards Committee of the British Society of Gastroenterology. U.K. guidelines on the management of variceal haemorrhage in cirrhotic patients. Gut. 2015 Nov;64(11):1680-704. https://www.ncbi.nlm.nih.gov/pubmed/25887380

[xx]Management of chronic hepatitis B infection: European Association for the Study of the Liver. EASL 2017 Clinical Practice Guidelines on the management of hepatitis B virus infection. J Hepatol. 2017 Aug;67(2):370-398. https://www.ncbi.nlm.nih.gov/pubmed/28427875

[xxi]Tenofovir: Marcellin P, Gane E, Buti M, Afdhal N, Sievert W, Jacobson IM, Washington MK, Germanidis G, Flaherty JF, Schall RA, Bornstein JD, Kitrinos KM, Subramanian GM, McHutchison JG, Heathcote EJ. Regression of cirrhosis during treatment with tenofovir disoproxil fumarate for chronic hepatitis B: a 5-year open-label follow up study. Lancet.2013;381:468–75.http://www.ncbi.nlm.nih.gov/pubmed/23234725

Tenofovir: World Health Organisation. Guidelines for the prevention, care and treatment of persons with chronic hepatitis B infection, March 2015. http://www.who.int/hiv/pub/hepatitis/hepatitis-b-guidelines/en/

[xxii] TAF – eGFR 15-50: Addendum: Use of TAF for adults with Hepatitis B (non-HIV co-infected (Addendum to original NDoH Evidence Summary: Use of TAF for adults with HIV v5.0_1July 2024

[xxiii]Metronidazole, oral: Ravdin JI. Amebiasis. Clin Infect Dis. 1995 Jun;20(6):1453-64; quiz 1465-6. Review.

http://www.ncbi.nlm.nih.gov/pubmed/7548493

Metronidazole, oral: Wuerz T, Kane JB, Boggild AK, Krajden S, Keystone JS, Fuksa M, Kain KC, Warren R, Kempston J, Anderson J. A review of amoebic liver abscess for clinicians in a nonendemic setting. Can J Gastroenterol. 2012 Oct;26(10):729-33. http://www.ncbi.nlm.nih.gov/pubmed/23061067

[xxiv] Ringers lactate -): Global Task Force on Cholera Control. October 2019.

National Institute for Communicable Diseases. Data on file, 2023

[xxv] Ciprofloxacin, oral (stat dose): National Institute for Communicable Diseases. Data on file, 2023.

Global Task Force on Cholera Control. October 2019.

[xxvi] Loperamide (max dose). Package Insert. Imodium. Johnson & Johnson (Pty) Ltd.Renewal of authorisation 04 March 2005.

[xxvii] Antibiotic therapy for CDI (metronidazole oral/IV, vancomycin, oral): McDonald LC, Gerding DN, Johnson S, Bakken JS, Carroll KC, Coffin SE, Dubberke ER, Garey KW, Gould CV, Kelly C, Loo V, Shaklee Sammons J, Sandora TJ, Wilcox MH. Clinical Practice Guidelines for Clostridium difficile Infection in Adults and Children: 2017 Update by the Infectious Diseases Society of America (IDSA) and Society for Healthcare Epidemiology of America (SHEA). Clin Infect Dis. 2018 Mar 19;66(7):987-994. https://www.ncbi.nlm.nih.gov/pubmed/29562266

Antibiotic therapy for CDI (metronidazole oral/IV, vancomycin, oral): Nelson RL, Suda KJ, Evans CT. Antibiotic treatment for Clostridium difficile-associated diarrhoea in adults. Cochrane Database Syst Rev. 2017 Mar 3;3:CD004610. https://www.ncbi.nlm.nih.gov/pubmed/28257555

Antibiotic therapy for CDI (metronidazole oral/IV, vancomycin, oral): Stevens VW, Nelson RE, Schwab-Daugherty EM, Khader K, Jones MM, Brown KA, Greene T, Croft LD, Neuhauser M, Glassman P, Goetz MB, Samore MH, Rubin MA. Comparative Effectiveness of Vancomycin and Metronidazole for the Prevention of Recurrence and Death in Patients With Clostridium difficile Infection. JAMA Intern Med. 2017 Apr 1;177(4):546-553. https://www.ncbi.nlm.nih.gov/pubmed/28166328

Antibiotic therapy for CDI (metronidazole oral/IV, vancomycin, oral): National Department of Health: Affordable Medicines, EDP-Adult Hospital level. Medicine Review: Systemic antibiotics for Enterocolitis due to Clostridium difficile, August, 2018. http://www.health.gov.za/

[xxviii] Metronidazole, oral: Marie C, Petri WA Jr. Amoebic dysentery. BMJ ClinEvid. 2013 Aug 30;2013. pii: 0918. http://www.ncbi.nlm.nih.gov/pubmed/23991750

Metronidazole, oral: Gonzales ML, Dans LF, Martinez EG. Antiamoebic drugs for treating amoebic colitis. Cochrane Database Syst Rev. 2009 Apr 15;(2):CD006085. http://www.ncbi.nlm.nih.gov/pubmed/19370624

CHAPTER 2
BLOOD AND BLOOD FORMING ORGANS

2.1 ANAEMIA

DESCRIPTION
Defined as a reduction in the absolute number of circulating red blood cells and most commonly diagnosed when the haemoglobin (Hb) concentration falls below the reference range for age and sex (Hb reference range males 13.0–17.0 g/dL; females 12.0–15.0 g/dL). The clinical features depend on the severity of anaemia, the rate at which it developed and the oxygen demands of the patient.

Anaemia can be classified according to the mean corpuscular volume (MCV) of the red blood cell (RBC) into macrocytic anaemia (MCV >100 fL), microcytic anaemia (MCV <80 fL), or normocytic anaemia (MCV 80–100 fL).

2.1.1 ANAEMIA, IRON DEFICIENCY
D50.0-1/D50.8-9

DESCRIPTION
Anaemia due to iron deficiency. Common causes of iron deficiency are chronic blood loss, poor iron absorption or poor nutritional intake.

Investigations
- » Low MCV and low MCH (mean corpuscular hemoglobin <26 pg) – note that these are often normal in early stages.
- » Full blood count (FBC) and peripheral smear: Hypochromic (low MCH) microcytic anaemia, and pencil cells often reported.
- » Confirm with low ferritin.
- » Investigate for cause of iron deficiency.
- » Consider upper and lower gastrointestinal endoscopies in high risk patients (all males and postmenopausal female patients) and patients not responding to treatment.

GENERAL MEASURES
- » Identify and treat the underlying cause.
- » Dietary adjustment if this is the underlying cause.

MEDICINE TREATMENT
Iron supplementation for treatment:

Oral iron preparation
- Ferrous sulfate compound BPC (dried), oral, 170 mg (± 55 mg elemental iron) 12 hourly. *LoE:IIIb*[i]

OR
- Ferrous fumarate, oral, 200 mg (± 65 mg elemental iron) 12 hourly.

- Do not ingest with tea, antacids or calcium supplements/milk.
- Doses should be taken on an empty stomach, but if gastrointestinal side effects occur, doses may be taken with meals.
- Continue with treatment for 3 months once Hb has normalised to replace iron stores.
- If daily iron is poorly tolerated (e.g. epigastric pain, nausea, vomiting and constipation), administer oral iron on alternate days with meals.

LoE:IIIb[ii]

Monitor patient response after one month of treatment: Hb should rise by at least 2 g/dL in the adherent patient without ongoing blood loss.

Consider the following if there is failure to respond to iron therapy:
» non-adherence,
» continued blood loss,
» alternate diagnosis,
» malabsorption, or
» mixed deficiency; concurrent folate or vitamin B_{12} deficiency.

Consult a specialist for further workup and/or intravenous iron supplementation if patient is not responding to oral iron supplementation despite adherence and no ongoing losses.

Parenteral iron preparation
Parenteral iron is seldom required and may very rarely be associated with anaphylaxis. Hypotensive episodes may occur if the injection is administered too rapidly. *LoE:IVb[iii]*

Parenteral iron is only indicated in the following scenarios:
» oral iron is ineffective (defined as lack of response after three months of oral iron therapy);
» oral iron is not tolerated;
» oral iron is not expected to be effective, e.g. malabsorption, patients on haemodialysis and erythropoietin therapy; or
» iron deficiency anaemia from 36 weeks of pregnancy;

In people who require repeated therapy, the intravenous route is preferred.
Note: Use in consultation with a specialist.

The total iron dose to be administered is determined by haemoglobin and body weight (advisable to also reference product information):

$$0.66 \times Body\ weight\ (kg) \times (100 - \frac{(Hb\ \times 100)}{14.8})$$

- Iron, IV, e.g.:
- Iron sucrose, slow IV infusion, 200 mg in 200 mL sodium chloride 0.9%, over 30 minutes.
  - This preparation can be administered to a maximum frequency of 3 times a week until the total calculated iron dose has been given.
  - Test dose is not required, however, caution is advised with every dose of IV iron, even if previously well tolerated.
  - An initial total dose of 600 mg (administered in three divided doses) is usually adequate to raise the Hb to acceptable levels.

OR *LoE:IVb[iv]*

- Low molecular weight iron dextran, slow IV infusion, 100–200 mg, diluted in 100 mL 0.9% sodium chloride or 5% glucose solution.
  - Maximum infusion rate: 100 mL over 30 minutes (200 ml per hour).
  - Administer 2–3 times per week until calculated total iron requirements have been given.
  - If patient requires rapid delivery of iron to replenish iron stores, iron dextran may be administered as a total dose infusion up to a total replacement dose of 20 mg/kg body weight. Dilute dose in 500 mL 0.9% sodium chloride or 5% glucose solution and give over 4–6 hours.
  - Test dose is not required, however, caution is needed with every dose of IV iron, even if previously well tolerated.

LoE:IIIb[v]

Resuscitation equipment should be readily available to manage anaphylaxis.

Red cell concentrate transfusion

Indicated in patients with:

» severe anaemia leading to cardiac failure or severe dyspnoea;
» active, ongoing bleeding; or
» where correction of anaemia is required prior to performing an urgent invasive procedure or surgery.

Iron supplementation for prophylaxis:

O99.0/D50.0-1/D50.8-9/Z29.2

For example during pregnancy:

- Ferrous sulfate compound BPC (dried), oral, 170 mg (± 55 mg elemental iron) daily. *LoE:IIIb[vi]*

OR

- Ferrous fumarate, oral, 200 mg (± 65 mg elemental iron) daily.

Note:

» Do not ingest oral iron with tea, antacids or calcium supplements/milk.
» Doses should be taken on an empty stomach, but if gastrointestinal side effects occur, doses should be taken with meals.

If daily iron is poorly tolerated:
» Features of intolerance: epigastric pain, nausea, vomiting, and/or constipation.
» Oral iron preparations may be prescribed on alternate days. If still poorly tolerated, dosing may be modified and taken once weekly. (See table below for dosing.)

Iron preparation	Alternate day dosing	Once weekly dosing
Ferrous sulphate compound BPC (dried)	170 mg (±55 mg elemental iron), once on alternate days	340 mg (±110 mg elemental iron), once weekly
Ferrous fumarate	200 mg (±65 mg elemental iron), once on alternate days	400 mg (±130 mg elemental iron), once weekly

Table 2.1: Alternative oral iron supplementation dosing regimens

LoE:IIb[vii]

REFERRAL/CONSULTATION
» Ongoing anaemia despite reported adherence and optimal therapy.

2.1.2 ANAEMIA, MEGALOBLASTIC
D51.0-2/D51.2/D51.8-9/D52.0-1/D52.8-9/D53.1/D53.8-9

DESCRIPTION
» Anaemia caused by a deficiency of folate and/or vitamin B_{12}.
» Note that several medicines can cause macrocytic anaemia (e.g. hydroxyurea, methotrexate, zidovudine, azathioprine, valproate, and phenytoin) without deficiencies of folate and/or vitamin B_{12}.
» Clinical manifestations of vitamin B_{12} deficiency are mainly neurological – peripheral neuropathy, dementia and subacute combined degeneration of the spinal cord.

Investigations
» Elevated MCV (>100 fl) and MCH (>34 pg).
» Pancytopaenia in severe cases.
» FBC and peripheral smear: oval macrocytes, hypersegmentation of neutrophils, thrombocytopenia with giant platelets.
» Decreased serum vitamin B_{12} and/or red blood cell folate.
» Intrinsic factor antibodies, and/ or anti-parietal cell antibodies are found in pernicious anaemia.

GENERAL MEASURES
» Counsel on dietary modifications to ensure adequate intake of folate and vitamin B_{12} (especially important in vegetarians and malnourished patients).

» Identify and treat the underlying cause, e.g. antibiotics for bacterial intestinal overgrowth.
» Chronic metformin use can lead to vitamin B_{12} deficiency by interfering with absorption. Maintain a low threshold for clinical features of vitamin B_{12} deficiency in patients on metformin, and check serum levels if clinically indicated.

MEDICINE TREATMENT

» Start with folic acid and vitamin B_{12} supplementation after taking blood samples for RBC folate and serum vitamin B_{12} levels.
» Monitor serum potassium and replace if necessary.
» Adjust management according to results.

CAUTION

Give vitamin B_{12} and folic acid together until the test results are available, as giving folic acid alone in patients with a vitamin B_{12} deficiency may precipitate a permanent neurological deficit.

Folic acid deficiency

- Folic acid, oral, 5 mg daily until Hb returns to normal (see reference ranges in Section 2.1: Anaemia).

Note: Prolonged treatment may be required for malabsorption states.

Vitamin B_{12} deficiency

For uncomplicated pernicious anemia:

- Vitamin B_{12}, IM, 1 mg on alternate days for 1–2 weeks.
  - Followed by 1 mg weekly until blood count is normal.
  - Lifelong maintenance dose: 1 mg monthly.

For serious complications from deficiency:

- Vitamin B_{12} IM, 1 mg daily for 1 week.
  - Followed by 1 mg weekly for 1 month.
  - Lifelong maintenance dose: 1 mg monthly.

LoE:IVb[viii]

Note:

» Response to treatment is associated with an increase in energy, strength and improvement in sense of well-being.
» Reticulocytosis begins 3–5 days after therapy and peaks at about day 7.
» Anaemia normally corrects within 1–2 months. The white cell count and platelets normalise in 7–10 days. As there is an increase in red blood cell production, iron and folic acid supplementation is also recommended until Hb has normalised.
» Monitor for hypokalaemia in the first few days of therapy. (See Section 7.2.2: Hypokalaemia for management.)

Consider the following in the event of response failure:
» Co-existing folate and/or iron deficiency,
» Other causes of macrocytosis:
  - Myelodysplasia.
  - Hypothyroidism.
  - Chronic alcohol use.
» Drug-induced, e.g. hydroxyurea, methotrexate, zidovudine, azathioprine, valproate and phenytoin.

Prophylaxis: O99.0/Z49.1/Z29.2
Vitamin B_{12} prophylaxis:
Vitamin B_{12} is indicated for patients after total gastrectomy or ileal resection:
- Vitamin B_{12}, IM, 1 mg every second month for life.

Folic acid prophylaxis:
Indications:
» Chronic inherited or acquired haemolytic anaemias, e.g. sickle cell anaemia, thalassaemia.
» Myeloproliferative disorders.
» Exfoliative skin disorders.
» Increased demands, e.g. pregnancy, chronic haemodialysis.
- Folic acid, oral, 5 mg daily.

2.1.3 ANAEMIA, CHRONIC DISORDER
D63.0/**D63**.8

DESCRIPTION
Anaemia due to chronic inflammation. This is characteristically a normochromic normocytic anaemia. Common causes of anaemia of chronic disorder include:
» Malignancy, e.g. haematological or solid tumours.
» Autoimmune disorders, e.g. rheumatoid arthritis.
» Chronic infections, e.g. HIV and TB.
» Chronic kidney disease.

GENERAL MEASURES
» Investigate and treat the underlying condition.
» Transfusion is seldom necessary.
» Do not treat with iron, folic acid or vitamin B_{12} unless there is a documented deficiency (note that diagnosing iron deficiency is difficult in chronic disorders as ferritin increases and serum iron decreases due to the acute phase response). A transferrin saturation level less than 20% usually indicates a combination of iron deficiency anaemia and anaemia of chronic disease.

2.1.4 ANAEMIA, HAEMOLYTIC

D55.0-3/D55.8-9/D56.0-4/D56.8-9/D58.0-2/D58.8-9/D59.0-6/D59.8-9

DESCRIPTION

Anaemia due to destruction of red blood cells. Destruction may be due to:

» Extracellular factors such as auto-immunity or mechanical factors, e.g. disseminated intravascular coagulation (DIC), hypersplenism, mechanical heart valves.
» Abnormalities of the cell membrane, e.g. hereditary spherocytosis.
» Enzymes, e.g. G6PD deficiency.
» Haemoglobin abnormalities, e.g. sickle cell anaemia, thalassaemia.
» Thrombotic thrombocytopaenic purpura (TTP) is a life-threatening emergency. Refer immediately to a specialist unit for plasma infusion or exchange (see Section 2.6: Thrombotic thrombocytopenic purpura-Haemolytic uraemic syndrome).

Investigations

» Evidence of haemolysis: anaemia, reticulocytosis, decreased haptoglobin, increased lactate dehydrogenase (LDH) and unconjugated hyperbilirubinaemia.
» FBC and peripheral smear: spherocytes often reported.
» Coombs' test (direct antiglobulin) is usually positive with autoimmune haemolysis.
» HIV status.

GENERAL MEASURES

» Treat the underlying cause.
» Do not transfuse prior to conducting appropriate investigations unless anaemia requires immediate intervention.
» In situations of life-threatening anaemia, transfuse the most compatible unit of red blood cells and get specialist advice urgently. Coombs-positive haemolytic anaemia may be technically difficult to cross match.
» Efficacy of transfusion is limited by the shortened red cell survival due to haemolysis.
» In G6PD deficiency, avoid drugs known to cause haemolysis, such as aspirin, sulphonamides (including co-trimoxazole), dapsone, methylene blue, and primaquine.
» In patients with cold agglutinins, all transfusions must be given through a blood warmer to avoid cold-induced haemolysis.

MEDICINE TREATMENT

Because of high red cell turnover, supplement with:

- Folic acid, oral, 5 mg daily.

Autoimmune haemolytic anaemia
Treat under specialist supervision.

LoE:IIb[ix]

- Prednisone, oral.
  - Initial dose: 1 mg/kg daily, until Hb is stable and >10 g/dL.
  - Taper slowly and monitor Hb at least once weekly. (Refer to Appendix II for an example of a dose reduction regimen.)
  - Glucocorticoids should be tapered slowly upon normalization of the haemoglobin and LDH. The patient should be monitored for recurrence following cessation of treatment.
  - As these conditions can often be life-threatening, specialist advice should be sought as early as possible after diagnosis.

REFERRAL/CONSULTATION

Indications of inadequate response:
» Haemolysis remains severe after 3 weeks of prednisone dosed at 1 mg/kg.
» Remission cannot be maintained on low doses of prednisone.
» The patient has intolerable adverse effects or contraindications to glucocorticoids.

Refer to specialist for second-line treatment:
» Immunosuppresive therapy – For specialist initiation.
» Splenectomy: Requires vaccination – see Chapter 11: Surgical prophylaxis.

LoE:IIIb[x]

2.1.5 ANAEMIA, APLASTIC

D60.0-1/D60.8-9/D61.0-3/**D61**.8-9

DESCRIPTION

Pancytopenia due to a hypoplastic bone marrow.

Clinical features:
» Pallor
» Petechiae
» Frequent or severe infections
» Purpura
» Bleeding

Pancytopenia in PLHIV B23.2 + (D61.2/D61.9)
Most common causes include:
» Direct effect of HIV.
» Medication (e.g. carbamazepine, valprote , phenytoin or pure red cell aplasia with emtricitabine and lamividine).
» Secondary opportunistic infections.
» Malignancies and nutritional deficiencies.
Many cases are idiopathic.

Investigations
» FBC and peripheral smear, Vitamin B_{12}, and red cell folate.
» Appropriate investigation to exclude opportunistic infections.
» Bone marrow trephine and aspiration in selected patients: where no other cause is found, in patients with persistent pancytopaenia, or to exclude infiltration with opportunistic infections, malignancies.

MEDICINE TREATMENT
If neutropenic and febrile, see Section 2.2: Febrile neutropenia.

REFERRAL
» Discuss all cases of suspected aplastic anaemia with a specialist. (If necessary, stabilise patient with blood products in preparation for transport after consultation with an expert.)

2.1.6 ANAEMIA, SICKLE CELL
D57.0-3/D57.8

DESCRIPTION
Sickle cell disease (SCD) is a genetic, inherited condition resulting in abnormal red blood cells. Homozygous SCD is the commonest and most severe form, characterised by recurrent vaso-occlusive episodes ("sickle crises") and chronic haemolytic anaemia. Adults develop hyposplenism, predisposing them to infection with encapsulated bacteria. Heterozygous SCD includes Haemoglobin S-C disease/HbSC, causing milder sickle cell disease, and sickle cell trait/HbS, who are generally asymptomatic.

VASO-OCCLUSIVE EPISODES
Vaso-occlusion can involve any part of the body, especially bone. Episodes may be triggered by dehydration, infection, stress or menstruation. The most common presentation is with acute episodes of pain that vary in severity, in the affected areas.

Investigations
» The diagnosis is suspected from the history, peripheral blood examination, and/or screening tests for sickling.
» Diagnosis is confirmed on haemoglobin electrophoresis.

GENERAL MEASURES
Severe vaso-occlusive episodes
» Keep well hydrated with intravenous fluids.
» Transfusion is only indicated for episodes with severe anaemia – discuss with a specialist.

MEDICINE TREATMENT

Severe vaso-occlusive episodes

» Maintain adequate saturation with oxygen supplementation.

To prevent venous thromboembolism:

- Low molecular weight heparin (LMWH), e.g.:
- Enoxaparin, SC, 40 mg daily.

OR

- Unfractionated heparin, SC, 5 000 units 12 hourly. *LoE:IIIb*[xi]

In morbid obesity dosing of LMWH should be individualised, in discussion with a specialist. *LoE:IIIa*[xii]

In renal failure (eGFR <30 mL/minute), the recommended prophylactic dose of enoxaparin is 20 mg daily. *LoE:IVb*[xiii]

Analgesia

» Control pain adequately – See Section 26.2.1: Medical conditions associated with severe pain.

Chronic management

All patients:

- Folic acid, oral, 5 mg daily.
- Vaccination against infections due to pneumococci and haemophilus influenza type B.

Management of severe vaso-occlusive episodes:

» Indications for treatment:
  - frequent painful vaso-occlusive episodes,
  - severe vaso-occlusive episodes (e.g. acute chest syndrome, stroke),
  - severe symptomatic anemia.

» Hydroxyurea is the mainstay of therapy in severe disease – refer for specialist initiation.

REFERRAL

» All patients, for chronic management in a specialised centre.

» Vaso-occlusive episodes should be managed in consultation with a specialist.

2.2 FEBRILE NEUTROPENIA

D70

DESCRIPTION

Febrile neutropenia is conventionally defined as an absolute neutrophil count of <0.5 x 10^9/L with a temperature of greater than 38°C for >1 hour or a single temperature of 38.3°C, but any neutropaenic patient showing clinical signs of sepsis should be investigated.

Note:

» **This is a medical emergency:** A minor infection may progress rapidly, with patients developing features of severe sepsis (multi-organ failure and/or hypotension). It is crucial to monitor and treat patients for signs and symptoms of infection.

» **Cultures should be obtained for appropriate microbiological testing prior to starting empirical antimicrobial therapy.**

» It is critical to recognise neutropenic fever early and to initiate empiric systemic antibacterial therapy promptly to reduce the risk of severe sepsis and mortality.

LoE:IVb[xiv]

GENERAL MEASURES

» Treat the underlying cause of neutropenia, if applicable.

» Withdraw any medication that may cause neutropenia, e.g. carbimazole, clozapine, co-trimoxazole, penicillins, carbamazepine, valproate.

» Consider removing central IV line. Once culture results are available, adjust treatment to the most appropriate narrow spectrum agent.

MEDICINE TREATMENT

For patients with febrile neutropenia within 48 hours of admission:

- Ceftriaxone, IV, 1 g daily. W

AND

- Gentamicin, IV, 6 mg/kg daily. A (See Appendix II for guidance on prescribing.)

<u>If IV line, and skin infection is suspected as the cause:</u>

ADD:

- Vancomycin, IV, 25–30 mg/kg as a loading dose. W Follow with 15–20 mg/kg/dose 12 hourly. (See Appendix II: Guidance on prescribing and monitoring.)

For patients with febrile neutropenia that develop after 48 hours of admission:

There is an increased risk of a hospital acquired infection. The choice of antibiotic will depend on local susceptibility patterns.

Regimen 1:

- Carbapenem with activity against Pseudomonas, e.g.:
- Meropenem, IV, 1 g 8 hourly. W

OR

- Imipenem/cilastatin, IV, 1000/1000 mg 8 hourly. W

Note: Ertapenem is not recommended as it is not effective for *Pseudomonas* species, which are important pathogens in this setting.

OR

Regimen 2:

- Piperacillin/tazobactam, IV, 4.5 g 6 hourly. W

AND LoE:IVb[xv]

- Amikacin, IV, 15 mg/kg daily. A (See Appendix II, for individual dosing and monitoring for response and toxicity.) LoE:IIIb[xvi]

OR

Regimen 3:

- Cefepime, IV, 2 g 12 hourly. W LoE:IVb[xvii]

If no response to antibiotics after 5–7 days: (In discussion with a Clinical Haematologist or Infectious Disease specialist)

ADD:

- Amphotericin B, IV, 1 mg/kg daily in dextrose 5% over 4 hours.
  - Ensure adequate hydration to minimise nephrotoxicity (see Appendix II for preventing, monitoring and management of toxicity).

Duration of therapy:

» If neutrophil count increases to >0.5 $\times$ 10^9/L, continue for 2 days after fever has settled.

» If neutrophil count remains $\leq$0.5 $\times$ 10^9/L, continue for 7 days after fever has settled.

REFERRAL/CONSULTATION

» All cases – consult with haematologist/oncologist.

2.3 MYELODYSPLASTIC SYNDROMES

D46.0-7/D46.9

DESCRIPTION

A group of disorders characterised by refractory cytopaenias due to bone marrow failure. There is a risk of disease progression to acute leukaemia.

Investigations
» Evidence of cytopenia, with normal vitamin B_{12} and folate levels, and often substantial morphological dysplasia on the peripheral smear.
» Bone marrow examination confirms dysplasia of the blood elements and the presence of cytogenetic abnormalities.

GENERAL MEASURES
» Transfusion should ideally be with leucodepleted red cells to delay sensitisation, as these patients require frequent transfusions.
» Bone marrow transplantation can be curative in selected patients.
» If neutropenic and febrile, see Section 2.2: Febrile neutropenia.

REFERRAL
» All patients for further investigation and management.

2.4 BLEEDING DISORDERS

GENERAL PRINCIPLES
A bleeding tendency may result from:
» a coagulation defect (congenital/acquired),
» a vessel wall defect, or
» a platelet defect (quantitative/qualitative).

A careful and detailed history, thorough examination and review of relevant laboratory investigations will allow differentiation between these three categories, as the management of each of these groups differs significantly.

Screening tests include: FBC, prothrombin time (PT) and activated partial thromboplastin time (aPTT; if prolonged, mixing studies are required).

Patients with a chronic bleeding tendency should be advised to wear a medic alert bracelet which clearly mentions the type of disorder he/she suffers from, e.g. severe Haemophilia A, Factor VIII <1%, no inhibitors.

2.4.1 HAEMOPHILIA A AND B
D66.7/D66.8

DESCRIPTION
Haemophilia A and B are lifelong chronic bleeding disorders caused by a lack of clotting factor VIII and clotting factor IX, due to mutations in the Factor VIII and Factor IX genes respectively. Acute bleeding presentation depends on the severity of the condition (see classification below). Bleeding can occur into any tissue, but intraarticular bleeds are the clinical hallmark of haemophilia.

Haemophilia complications include haemarthrosis that may lead to chronic arthropathy, intracranial haemorrhage, soft tissue and muscle haematomas.

In a known person with haemophilia, pain/tingling in a joint suggests early-onset bleeding.

Early consultation and regular follow-up with a haematologist or clinician with expertise in managing such patients is advisable. All patients diagnosed with haemophilia should attend a designated specialised Haemophilia Treatment Centre with a dedicated multi-disciplinary health care team at least annually for adults. The details of available Haemophilia Treatment Centres can be accessed at*: https://haemophilia.org.za/haemophilia-treatment-centres-htcs/*. All patients diagnosed with haemophilia should be enrolled in the South African Bleeding Disorders Registry (access relevant co-ordinators at: *https://haemophilia.org.za/haemophilia-nurses-office/*).

Those eligible for prophylaxis with factor VIII or IX (see below) may receive factor replacement therapy at a healthcare facility twice a week. Where appropriate, home-based care can be considered.

Haemophilia severity classification

Class	Clotting factor	Factor level	Signs
Mild	VIII or IX	> 5 – <40%	Occasional bleeds, usually after trauma or surgery.
Moderate	VIII or IX	1–5%	Less frequent bleeds than severe; usually post trauma/surgery/dental extraction. Some patients may, however, display a severe bleeding phenotype.
Severe	VIII or IX	< 1%	Spontaneous bleeds, particularly joint and muscle.

Table 2.2: Classification of haemophilia severity
(Adapted from White et.al. Journal of Thrombosis *and* Haemostasis. *2001)*[xviii]

DIAGNOSTIC CRITERIA

Clinical

» Major bleeds:
  - central nervous system (CNS) – intracranial
  - severe injury
  - muscle compartment (e.g. forearm and calf)
  - gastrointestinal tract
  - neck/throat (airway)
  - advanced joint and soft tissue
  - hip and ilio-psoas muscle

» Minor bleeds:
  - early joint bleed
  - soft tissue
  - mouth and gum
  - muscle
  - epistaxis
  - haematuria

» Pain/tingling in a joint of a patient with haemophilia suggests bleeding.

Investigations

Baseline

» Normal white cell count and platelets; may have anaemia due to blood loss or iron deficiency.
» Normal INR.
» Prolonged activated partial thromboplastin time (aPTT).
» APTT correction studies.
» Factor VIII or IX plasma levels < 50%.
» HIV, hepatitis B, and hepatitis C testing if status not known.

Non-responders to factor replacement or those previously diagnosed with inhibitors

» Inhibitor screen (Bethesda or Nijmegen assays).

GENERAL MEASURES

» Patient, family and community education.
» Enrolment in the South African Bleeding Disorders Registry (access relevant co-ordinators at*: https://haemophilia.org.za/haemophilia-nurses-office/)*.
» MedicAlert bracelet (or similar).
» Dental care (see below for management of tooth extraction).
» Avoid contact sport.

Exercise great caution when taking blood specimens (no arterial samples).
Taking blood from femoral veins is contra-indicated.
Do not insert or use central lines unless done as part of life-saving efforts.
Do not aspirate joints.
Avoid IM injections.
Avoid aspirin and other NSAIDs.

MEDICINE TREATMENT

Treatment approaches are divided into two main categories: prophylaxis and on demand (episodic) treatment following a bleed.

Prophylaxis

Prophylaxis aims to prevent the number of bleeds and prevent or delay the development of joint arthropathy and other sequelae. Primary and secondary prophylaxis can be considered in consultation with a Haemophilia Treatment Centre.

In consultation with a Haemophilia Treatment Centre, prophylaxis is sometimes needed in patients presenting with a target joint.

Treatment on Demand (episodic treatment)

Episodic treatment for bleeding episodes is referred to as on demand therapy (i.e. the use of factor replacement therapy when bleeding occurs).

Home treatment
Haemophilia Treatment Centres promote home treatment of bleeds. Patients or caregivers must be educated on the storage, reconstitution and administration of clotting factor concentrate and provided with a supply of clotting factor concentrate to be kept at home for use in case of a bleed and/or for prophylaxis. Clotting factor concentrate use and bleeding episodes are monitored through an appropriate chart (or bleeding diary), which can be reviewed at consultations and medication collection.

ACUTE MANAGEMENT OF BLEEDS

For pain (as required):
Refer to Section 26.2.1 Medical conditions associated with severe pain and Section 12.4.2: Postoperative pain in the recovery room.

Do not use NSAIDs, including aspirin.

For bleeding episodes
Emergency treatment while awaiting transfer, if indicated.
If serious bleeding in a known patient with haemophilia, and no factor is available:

- Lyophilised plasma (FDP), IV, 15 mL/kg over 20-30 minutes. Lyophilised plasma contains a minimum of 0.4 units/mL of each coagulation factor.

OR *LoE:IIIb*[xix]

- Fresh Frozen Plasma (FFP), IV, 15 mL/kg over 20-30 minutes.

Acute joint bleeds – Infuse intravenous factor concentrate first (refer to Section 2.4.1.1 or Section 2.4.1.2 below for dosing guidance) with the following adjunctive measures:

» Apply ice packs: 5 minutes on and 10 minutes off.
» Rest the affected joint/limb until pain-free and there is no further swelling.
» Avoid weight-bearing.
» Splint. Do not use circumferential casts.
» **Do not** aspirate affected joints.
» Do not request an X-ray of the affected joint unless there is a strong suspicion of fracture.

Give clotting factor concentrate until the patient is pain-free and the joint's range of motion is normal. Administration should be 12 hourly (for Haemophilia A) for major bleeds but may be daily for minor bleeds.

For mucous membrane bleeds

- Tranexamic acid, oral, 1 - 1.5 g (15 - 25 mg/kg) 6-8 hourly.

For dental extraction/male circumcision/minor surgical procedures
Check that inhibitors are absent.
Admit for the procedure and post-procedure care and observation in a facility with experience in haemophilia management.
Haemophilia A:

- Factor VIII, intravenous, 40 units/kg, immediately before extraction.

AND

- Tranexamic acid, oral, 25 mg/kg/dose 6–8 hourly, starting 2 hours before the procedure and continued for 5 days post-procedure.

Haemophilia B:

- Factor IX/factor IX complex, intravenous, 40 units/kg, immediately before extraction.

Ideally, elective surgery should be performed at a tertiary/quaternary centre in consultation with a clinical haematologist.
In emergencies, treat it as a major bleed and consult the local Haemophilia Treatment Centre as soon as feasible.

2.4.1.1 HAEMOPHILIA A - FACTOR VIII DEFICIENCY (NO INHIBITORS)

D66

PROPHYLAXIS

Prophylaxis (primary and secondary) should be considered for patients with severe haemophilia A (<1% factor activity) who can access the health facility twice weekly for infusions; or have indwelling venous catheters or are candidates for home-based care.

Primary prophylaxis: Prophylaxis started in the absence of documented joint disease/damage.
Secondary prophylaxis: Prophylaxis initiated after joint damage has occurred.

- Factor VIII, intravenous 25 units/kg, twice weekly.
  - The clotting factor should be rounded to the nearest full vial to avoid wastage.
  - Proposed rounded dosing (see table below):

Factor VIII dosing table				
Age in years	**Average weight (kgs)**	**IU required per dose**	**Rounded dose (IU)**	**Available products**
>12 (adults)	50	1250	1300	2 x 500IU plus 1 x 300IU
>12 (adults)	60	1500	1500	3 x 500IU
>12 (adults)	70	1750	1800	3 x 500IU plus 1 x 300IU

TREATMENT ON DEMAND

Minor bleeds:

Bleeds into the muscle or soft tissue, mouth or gums, epistaxis, painless haematuria and early joint bleeds.

- Factor VIII, intravenous, 20 - 40 units/kg.
  - If there is evidence of ongoing bleeding after 12 hours, consult with local haemophilia treatment centre.

Major bleeds:

Advanced muscle or joint bleeds result from severe injury or bleeds that affect the central nervous system, gastrointestinal system, neck or throat, hip or iliopsoas muscle, or forearm compartment.

LoE: III[xx]

- Factor VIII, intravenous, 40 - 50 unit/kg.
  - Use all the contents of the appropriate volume ampoule.
  - All of these patients need hospitalisation.
  - Discuss all patients promptly with the local Haemophilia Treatment Centre.

Intracranial bleeds (*paediatrics and adults*)

- Factor VIII, intravenous, 40 – 50 units/kg 6 hourly.
  - Decrease frequency of dosing if the trough factor level is > 50%, if possible.

2.4.1.2 HAEMOPHILIA B - FACTOR IX DEFICIENCY (NO INHIBITORS)

D67

PROPHYLAXIS

Prophylaxis (primary and secondary) should be considered for patients with severe haemophilia B (<1% factor activity) who can access the health facility twice weekly for infusions; or have indwelling venous catheters or are candidates for home-based care.

Primary prophylaxis: Prophylaxis started in the absence of documented joint disease/damage.
Secondary prophylaxis: Prophylaxis initiated after joint damage has occurred.

- Factor IX, intravenous 25 units/kg, twice weekly.

TREATMENT ON DEMAND

Minor bleeds

Bleeds into the muscle or soft tissue, mouth or gums, epistaxis, painless haematuria and early joint bleeds.

- Factor IX/factor IX complex, intravenous, 40 units/kg immediately as a single dose.
  - If there is evidence of ongoing bleeding after 12 hours, consult with local haemophilia treatment centre.

Major bleeds
Major muscle or joint bleeds result from severe injury or bleeds that affect the central nervous system, gastrointestinal system, neck or throat, hip or iliopsoas muscle, or forearm compartment.

- Factor IX/factor IX complex, intravenous, 60 units/kg. *LoE: III*[xxi]
  - All these patients need hospitalisation.

Discuss all patients promptly with the local Haemophilia Treatment Centre to plan ongoing treatment and factor replacement.

2.4.1.3 HAEMOPHILIA WITH INHIBITORS

Refer for assessment and planning with a haematologist.

REFERRAL
» All cases with **suspected** or established haemophilia (prolonged PTT and normal INR), for assessment, genetic counselling and planning of management, to a Haemophilia Treatment Centre.

2.4.2 VON WILLEBRAND DISEASE
D68.0

DESCRIPTION
Von Willebrand disease is the most common congenital bleeding disorder and is due to reduced amounts or abnormal forms of von Willebrand factor.

DIAGNOSTIC CRITERIA
Clinical
» Recurrent epistaxis, prolonged bleeding from lacerations, easy bruising or gum bleeds.

Investigations
» Reduction in one or more of the following:
- von Willebrand factor antigen,
- Ristocetin co-factor or collagen binding activity,
- factor VIII coagulant activity.

GENERAL AND SUPPORTIVE MEASURES
» Apply pressure to the bleeding site.
» For tooth socket bleeds, bite down on a piece of gauze.

CAUTION
Avoid aspirin and other NSAIDs.

MEDICINE TREATMENT

Mild bleeding

Such as epistaxis and menorrhagia.

- Antifibrinolytics, e.g.:
- Tranexamic acid, oral, 1 g 6-8 hourly.

Recurrent menorrhagia can also be treated effectively with oral contraceptives. See Section 5.2: Uterine bleeding, abnormal.

More severe mucous membrane bleeding

Consult a local haemophilia treatment centre.

During surgery or after major trauma, patients should receive:

- Factor VIII (Factor VIIII-containing von Willebrand factor VIII), IV, 30 IU/kg/dose given every 12 hours.
  - Continue for 48–72 hours to ensure optimal haemostasis.
  - For major surgical procedures, use for 7–10 days. *LoE: IVb*

REFERRAL

» All suspected cases of von Willebrand disease to a Haemophilia Treatment Centre for assessment.
» Symptomatic thrombocytopenia.

2.5 IMMUNE THROMBOCYTOPENIA (ITP)

D69.3

DESCRIPTION

A common bleeding disorder due to immune-mediated destruction of platelets. Clinically apparent associated conditions, drugs (e.g. penicillins, cephalosporins, quinine, rifampicin and heparin), or other agents that may cause thrombocytopenia must be excluded before a diagnosis of ITP can be considered. Patients with suspected ITP should be tested for SLE and for HIV infection.

Investigations:

» Thrombocytopenia with normal white cell count and red cell indices (however, anaemia may be present due to blood loss).
» Peripheral blood smear to exclude RBC fragments. Smear may show large platelets.
» Do INR and aPTT, both of which should be normal in ITP.
» If there is poor response to treatment, to do a bone marrow aspirate and biopsy.

GENERAL MEASURES

» Avoid:
  – medication that affects platelet function, e.g. NSAIDs and aspirin,
  – platelet transfusions, unless there are life-threatening bleeds,

- unnecessary treatment of asymptomatic patients with mild to moderate thrombocytopenia (platelet count >30 x 10^9/L).
- dental procedures in acute phase, and
- intramuscular injections.

» Reassure the patient that resolution usually occurs in acute ITP.
» Medic alert bracelet.
» Platelet transfusions may be given if surgery is required or in life-threatening bleeding: discuss with haematologist.
» Goal of treatment is to reduce the risk of bleeding rather than to normalise the platelet count.

MEDICINE TREATMENT

Acute ITP

- Prednisone, oral, 1 mg/kg daily until platelet count has normalised.
  - Taper slowly and monitor platelet count. (Refer to Appendix II for an example of a dose reduction regimen.)
  - Although prednisone is also indicated for HIV-associated immune thrombocytopenia, it is important that these patients should be fast-tracked for antiretroviral therapy (ART) – See Section 10.1: Antiretroviral therapy.

LoE:IIb[xxii]

Acute life-threatening bleeding and surgery

- Platelet transfusion, intravenous, 1 unit immediately.
  - Platelet transfusions are only indicated in acute active bleeding uncontrolled by other means or before procedures.
  - In an adult, 1 unit of platelets (preferably single donor, leucocyte depleted) is usually sufficient to control the bleeding initially.
  - Platelet transfusions have limited benefit in this condition as platelets are rapidly destroyed by the immune system.
- Methylprednisolone acetate 1 g, IV, daily for 3 days. *LoE:IIIb*[xxiii]

REFERRAL

» All cases not responding to steroids that require second line treatment - Consult haematologist.
» All PLHIV who are not responding to ART - Consult haematologist

2.6 THROMBOTIC THROMBOCYTOPENIC PURPURA-HAEMOLYTIC URAEMIC SYNDROME (TTP-HUS)

D59.3 + (M31.1)

DESCRIPTION

» Acute syndromes with abnormalities in multiple organ systems and evidence of micro-angiopathic haemolytic anaemia and thrombocytopenia.

» This condition presents with varying combinations of the following (only some of which may be present):
  – Microangiopathic haemolytic anaemia and thrombocytopenia, often with purpura but not usually severe bleeding,
  – acute renal insufficiency,
  – neurologic abnormalities, and/or
  – fever.
» Note: The presence of fragments and low platelets is enough to consider the diagnosis.
» Microangiopathic haemolytic anaemia is defined as non-immune haemolysis with prominent RBC fragmentation (schistocytes) observed on the peripheral blood smear along with thrombocytopaenia.
» TTP-HUS is often associated with HIV infection and all patients should be tested for HIV.
» TTP-HUS should be distinguished from disseminated intravascular coagulation (DIC) and severe pre-eclampsia where, in the latter, the coagulation profile (PT/PTT) is also deranged.

MEDICINE TREATMENT

» **This is a medical emergency.**
» In HIV-associated thrombotic thrombocytopenia, start combination antiretroviral therapy urgently.
» Platelet transfusions may be associated with increased morbidity and mortality. Use of platelet transfusions should be discussed with a specialist.

Transfusion of plasma products:

- Lyophilised plasma, IV infusion, 30 mL/kg/day in 3–4 divided doses.

OR

- Fresh frozen plasma, IV infusion, 30 mL/kg/day in 3–4 divided doses.

LoE:IIIb[xxiv]

REFERRAL

» All patients – discuss with a haematologist urgently.

2.7 ACQUIRED COAGULATION DEFECTS

2.7.1 DISSEMINATED INTRAVASCULAR COAGULATION (DIC)

D65/D68.2/D68.8

DESCRIPTION

DIC is a complication of an underlying condition and is characterised by widespread activation of the clotting cascade which leads to consumption of clotting factors and platelets with generalized bleeding. No single diagnostic test, but the combination of a prolonged INR and PTT, presence of

thrombocytopenia, decreased fibrinogen and increased D-dimer is highly suggestive of the diagnosis.

GENERAL MEASURES

» Identify and treat the underlying cause.
» If the patient is bleeding, replace haemostatic factors with cryoprecipitate or FFP/lyophilised plasma.
» If the patient is not actively bleeding and platelet count >20 x 10^9/L, then platelet transfusion is not necessary.

MEDICINE TREATMENT

For severe thrombocytopaenia (<20 x 10^9/L) and/or active bleeding:

- Platelet transfusion (apheresis single donor or pooled random donor), IV, 1 unit, immediately.
  - In chronic DIC, or in the absence of bleeding, platelet transfusions should not be given merely to correct the thrombocytopenia.

For hypofibrinogenaemia:

- Cryoprecipitate, IV, 1 unit/10 kg.

For depletion of other coagulation factors:

- Lyophilised plasma, IV, 15 mL/kg as initial dose.
  - Volume: ±200 mL/unit.

OR

- Fresh frozen plasma, IV, 15 mL/kg as initial dose. *LoE:IIIb*[xxv]
  - Volume: ±280 mL/unit.

» Repeat replacement therapy 8 hourly or less frequently, with adjustment according to the clinical picture and laboratory parameters.
» Monitor response with frequent estimation of the platelet count and coagulation screening tests.

2.8 VENOUS THROMBO-EMBOLISM

I26.0/I26.9/I80.0-3/I80.8-9/I81/I82.0-3

DESCRIPTION

Venous thromboembolism (VTE) can occur at different sites, ranging from calf deep venous thrombosis (DVT) to pulmonary thrombo-embolism (PE). For VTE in pregnancy, see Section 2.8.3: VTE during pregnancy and the puerperium.

Differential diagnosis includes:

» cellulitis
» superficial thrombophlebitis
» lymphoedema
» chronic venous insufficiency
» ruptured popliteal (Baker's) cyst
» calf muscle pull or tear
» internal derangement of the knee

Diagnosis is primarily clinical and confirmed with imaging studies, e.g. Duplex Doppler.

GENERAL MEASURES

Strategies for prevention include:

» lifestyle modifications (e.g. prevention of obesity and inactivity),
» avoiding dehydration,
» avoiding cigarette smoking,
» maintaining normal blood pressure,
» mechanical measures like vascular compression stockings, and intermittent pneumatic compression boots.

LoE:IIIb[xxvi]

Acute management

Thrombolytic therapy may be indicated in patients with confirmed early pulmonary embolism where haemodynamic stability cannot be achieved: discuss with a specialist.

2.8.1 VENOUS THROMBO-EMBOLISM – PROPHYLAXIS

MEDICINE TREATMENT

Risk Assessement

Risk assessment is essential, and treatment needs to be individualised. Risk factors for VTE can be divided into predisposing factors (i.e. patient characteristics) and exposing factors (i.e. underlying medical conditions, nature of surgical intervention).

Predisposing risk factors	
Thrombophilia	Advanced age (>60 years)
History of VTE	Chronic cardiac insufficiency
Malignancy	Obesity (BMI > 30 kg/m^2)
Drugs, e.g. TB treatment, thalidomide	Oestrogen therapy
HIV infection	Nephrotic syndrome
Auto-immune disease	Varicose veins

Exposing risk factors		
Risk level	**Surgical patients**	**Medical patients**
Low VTE risk	» Surgery lasting <30 minutes » Injuries without or with only minor soft-tissue trauma » No or only minor additional predisposing risk factors	» Infection or acute inflammatory diseases without bed rest » Central venous catheters » No or only minor additional predisposing risk factors

Moderate VTE risk	» Surgical procedures of longer duration » Immobilisation of lower limb with plaster cast » Lower limb arthroscopic procedures » No or only minor additional predisposing risk factors	» Acute cardiac insufficiency (NYHA III/IV) » Acute decompensated COPD without ventilation » Infection or acute inflammatory diseases with bed rest » Malignant disease » No or only minor additional predisposing risk factors
High VTE risk	» Major surgical procedures for malignancy » Multiple trauma or severe trauma of the spine, vertebra or lower limbs » Major orthopaedic surgery, e.g. hip or knee replacement » Major surgical procedure in cardiothoracic and/or pelvic region	» Stroke with paralysis » Acute decompensated COPD with ventilation » Sepsis » ICU patients » Other conditions associated with debilitating illness

Table 2.3: VTE risk assessment in surgical and non-surgical patients
Modified from Source: Jacobson BF, Louw S, Büller H, Mer M, de Jong PR, Rowji P, Schapkaitz E, Adler D, Beeton A, Hsu HC, Wessels P, Haas S; South African Society of Thrombosis and Haemostasis. Venous thromboembolism: prophylactic and therapeutic practice guideline. S Afr Med J. 2013 Feb 15;103(4 Pt 2):261-7. https://www.ncbi.nlm.nih.gov/pubmed/23547704

For patients hospitalised due to medical illnesses at high risk of VTE:

- Rivaroxaban, oral, 10 mg daily while hospitalised. *LoE:Ib[xxvii]*

For patients hospitalised due to medical illnesses and in whom rivaroxaban is contraindicated (see summary table below):

- Low molecular weight heparin, e.g.:
- Enoxaparin, SC, 40 mg daily.
  - In morbid obesity, dosing of LMWH should be individualised, in discussion with a specialist.
  - Renal impairment (eGFR <30 mL/min): adjust dose to 20 mg daily.

OR *LoE:IVb[xxviii]*

- Unfractionated heparin, SC, 5 000 units 12 hourly.
  - Dose adjustment is generally not required for renal impairment.
  - Monitor for bleeding complications. *LoE:IIIb[xxix]*

For orthopaedic surgical patients with trauma-related i) operative extremity fractures or ii) operative and non-operative pelvic and acetabular fractures:

Low to moderate risk of VTE:

- Aspirin, oral, 150 mg daily. *LoE:IIb[xxx]*

- Initiate aspirin >12 hours post-operatively and continue for 14 days or until mobilisation.
- In patients with non-operative pelvic and acetabular fractures, prophylaxis can be continued for up to 35 days. If clinically appropriate (i.e. in the absence of clear evidence of VTE risk), discontinuation prior to 35 days, on discharge from hospital should be considered.

<u>High risk of VTE:</u> *LoE:III*

- Low molecular weight heparin, e.g.:
- Enoxaparin, SC, 40 mg daily.
  - In morbid obesity dosing of LMWH should be individualised, in discussion with a specialist.
  - Renal impairment (eGFR <30 mL/min): adjust dose to 20 mg daily.
  - In patients with non-operative pelvic and acetabular fractures, prophylaxis can be continued for up to 35 days. In the absence of clear evidence of VTE risk or on earlier discharge from hospital, discontinuation prior to 35 days should be considered.

For elective total hip arthroplasty:

- Rivaroxaban, oral, 10 mg daily.
  - Initated 6–10 hours post-surgery for duration of admission or a maximum of 10 days.

<u>Following rivaroxaban, prescribe aspirin:</u>

- Aspirin, oral, 150 mg daily for 28 days on discharge from hospital.

For elective total knee arthroplasty:

Total duration of prophylactic therapy: 14 days.

- Rivaroxaban, oral, 10 mg daily.
  - Initiate anticoagulation 6–10 hours post-surgery for the duration of hospital admission for a minimum of 2 days and a maximum of 7 days.

<u>Following rivaroxaban, prescribe aspirin:</u>

- Aspirin, oral 150 mg daily.
  - Treat with aspirin for remainder of VTE prophylaxis period, i.e. 14 days in total including days on rivaroxaban. *LoE:Ib*[xxxi]

For i) other surgical patients, or ii) orthopaedic surgical patients with a contraindication to aspirin or rivaroxaban:

- Low molecular weight heparin, e.g.:
- Enoxaparin, SC, 40 mg daily.
  - In morbid obesity, dosing of LMWH should be individualised, in discussion with a specialist.
  - Renal impairment (eGFR <30 mL/min): adjust dose to 20 mg daily.

OR *LoE:IVb*[xxxii]

- Unfractionated heparin, SC, 5 000 units 12 hourly. *LoE:IIIb*[xxxiii]
  - Dose adjustment generally not required for renal impairment.

- Monitor for bleeding complications.

The table below is a summary of the guidance for VTE prophylaxis:

	At risk population	VTE prophylaxis	Duration
Medical	Hospitalised patients with debilitating illness	Rivaroxaban, oral, 10 mg daily.	While hospitalised.
Orthopaedic Surgical	Total hip arthroplasty	Rivaroxaban, oral, 10 mg daily **followed by** aspirin, oral, 150 mg daily.	Rivaroxaban: From 6-10 hours post-op, for up to 10 days (or less if hospitalised <10 days). Aspirin: For 28 days on hospital discharge.
Orthopaedic Surgical	Total knee arthroplasty	Rivaroxaban, oral, 10 mg daily for 2-7 days, **followed by** aspirin, oral, 150 mg.	Rivaroxaban: From 6-10 hours post-op, for at least 2 days (max 7 days). Aspirin: Treat for remainder of VTE prophylaxis period, i.e. 14 days in total including days on rivaroxaban.
	Trauma-related **operative**: i) extremity fractures ii) pelvic and acetabular fractures	Low to moderate risk of VTE: Aspirin, oral, 150 mg daily. High risk of VTE: Enoxaparin, SC, 40 mg daily.	From >12 hours post-operatively, for 14 days or until mobilisation.
	Trauma-related **non-operative** pelvic and acetabular fractures	Low-moderate risk of VTE: Aspirin, oral, 150 mg daily. High risk of VTE: Enoxaparin, SC, 40 mg daily.	From admission up to 35 days.
Other Surgical	Other major surgery	Enoxaparin, SC, 40 mg daily. **OR** Unfractionated heparin, SC, 5 000 units 12 hourly.	While hospitalised.

Table 2.4: Summary of VTE prophylaxis in surgical and non-surgical patients

Although the risk of bleeding is small, prophylaxis should only be used under exceptional circumstances in patients with the following conditions:

» Active bleeding or high risk of active bleeding (eg. severe liver disease; peptic ulcer disease).
» Intraocular, intracranial or spinal surgery.
» Patients requiring lumbar puncture or spinal/epidural anaesthesia within 24 hours of rivaroxaban dose, within 12 hours of enoxaparin when used as prophylaxis, or within 24 hours of enoxaparin when used at therapeutic doses. For timing of anticoagulants – see Section 12.7.1: Anticoagulants and spinal or epidural blocks.
» Renal insufficiency: Rivaroxaban not recommended if eGFR<30ml/min; enoxaparin requires renal dose adjustment.
» Coagulopathy.
» Uncontrolled hypertension.
» Concomitant anticoagulations or antiplatelet therapy.

Additional contraindications to rivaroxaban not covered above:

Patient populations	Comorbidities	Drug interactions
Pregnancy Lactation Minors (<18 years of age) Patient weight >120 kg or BMI >40 kg/m^2 Age >65 years†	Known rivaroxaban hypersensitivity Antiphospholipid syndrome (persistent, triple positive) Previous bronchiectasis, pulmonary cavitation, or pulmonary haemorrhage Active malignancy‡	Drugs that ↑rivaroxaban: Ketoconazole, Ritonavir Drugs that ↓rivaroxaban: Phenytoin, carbamazepine, rifampicin, St. John's Wort

Table 2.5: Contraindications to rivaroxaban
†Insufficient evidence in this patient population.
‡Exception: Patients receiving extended prophylaxis after gynaecological or colorectal malignancies.

2.8.2 VENOUS THROMBO-EMBOLISM – ACUTE TREATMENT

MEDICINE TREATMENT

LoE:Ib[xxxiv]

For proximal deep venous thrombosis and/or pulmonary embolism:

- Rivaroxaban, oral, 15 mg twice daily for 3 weeks, followed by 20 mg once daily for 3 months.

If i) rivaroxaban is contraindicated, or ii) patient is high risk and requires long term anticoagulation (> 6 months), e.g. recurrent VTE:

» Start unfractionated or low molecular weight heparin simultaneously with warfarin.

» After 5 days, heparin may be stopped if an INR within therapeutic range (INR between 2 and 3) has been reached and maintained for at least 24 hours.
» Note: Heparin and warfarin therapy should overlap for at least 5 days.

▪ Low molecular weight heparin, e.g.:

- Enoxaparin, SC, 1.5 mg/kg daily, LoE:I[xxxv]
  OR
- Enoxaparin, SC, 1 mg/kg 12 hourly. LoE:I[xxxvi]

CAUTION – Enoxaparin

In morbid obesity, dosing of LMWH should be individualised in discussion with a specialist. LoE:III[xxxvii]

In renal failure (eGFR <30 mL/minute), the recommended treatment dose of enoxaparin is 1 mg/kg daily. LoE:III[xxxviii]

CAUTION – Unfractionated heparin

Evidence indicates that PTT monitoring is not necessary with weight-based dosing of unfractionated heparin. However, in patients with morbid obesity and renal failure (eGFR <30 mL/minute), unfractionated heparin should be used with PTT monitoring to maintain the PTT at 1.5 to 2.5 times the control.

PTT should be taken 4 hours after SC dose.

LoE:IVb

Follow with:

- Warfarin, oral, 5 mg daily.
  - Measure INR after 48 hours, then every 1 to 2 days until the INR is within the therapeutic range of 2–3 (refer to initiation dosing tables in the Appendix II).
  - Adjust dose to keep INR within therapeutic range (refer to maintenance dosing tables in Appendix II). LoE:IVb[xxxix]
  - Continue warfarin for 3 months with regular INR monitoring, provided that a precipitating cause that has resolved.
  - In patients with a first-time, unprovoked DVT, discuss duration of therapy with a specialist.
  - All women of reproductive age should be on appropriate contraception (see Primary Health Care STGs and EML, Chapter 7: Family Planning). If a pregnancy is planned, do frequent pregnancy tests and change to enoxaparin once pregnancy is confirmed (see Section 2.8.3: VTE during pregnancy and the puerperium). LoE:IIIb[xl]
  - For all major elective surgery and other elective procedures with a significant bleeding risk, such as neuraxial anaesthesia and lumbar punctures, the INR should be <1.5 (see Section 12.7.1: Anticoagulants and spinal or epidural blocks).

- Educate patient on signs and symptoms of warfarin toxicity, and on risks associated with drastic dietary changes such as increased consumption of cruciferous vegetables.

Heparin induced thrombocytopenia (HIT)
A severe immune-mediated drug reaction occurring in 1–5% of patients receiving heparin therapy (more common with unfractionated heparin, but may also occur with low molecular weight heparin). It presents with thrombocytopenia and thrombosis. Diagnosis requires a high index of suspicion and should be considered if a patient has a 50% drop in platelet count within 5–10 days after initiating heparin therapy. A positive antibody test confirms the diagnosis.

Management of HIT:
Stop heparin and discuss all patients with a specialist.

REFERRAL/CONSULTATION
» All patients with heparin induced thrombocytopaenia.

2.8.3 VTE DURING PREGNANCY AND THE PUERPERIUM
O22.2-3/O87.0-1/O87.9/O88.3

DESCRIPTION
The risk of VTE is substantially increased in pregnancy and is an important cause of maternal morbidity and mortality.

MEDICINE TREATMENT
Prophylaxis
Risk Assessement
A risk assessment should be done in pre/early pregnancy and repeated if the woman is admitted to hospital for any reason, during delivery, and immediately post delivery.

The decision to provide VTE prophylaxis will depend on an assessment of the patient's risk for thromboembolism:

Indications	Duration of therapy
Previous VTE episode (DVT or pulmonary embolism)	VTE prophylaxis during pregnancy and for up to 6 weeks post-delivery. *LoE:IIIb*[xii]
Patient with any **ONE** of the following high risk factors: » Emergency Caesarean section » BMI > 40 kg/m^2 » Prolonged hospital stay » Intravenous drug user	VTE prophylaxis for a minimum of 5 days post delivery (or longer duration if still admitted in hospital)

Indications	Duration of therapy
Patient with any of the following intermediate risk factors: » Age > 35 years of age. » BMI 35-40 kg/m^2. » Parity ≥ 3. » Smoker. » Elective caesarean section. » Any surgical procedure in the puerperium. » Gross varicose veins. » Current systemic infection. » Immobility e.g paraplegia, long distance travel. » Current pre-eclampsia. » Prolonged labour > 24 hours. » PPH† > 1 litre or requiring blood transfusion.	**One** risk factor: Prevent dehydration and encourage early mobilisation. **Two or more** risk factors: VTE prophylaxis for a minimum of 5 days post delivery (or longer duration if still admitted in hospital).

†Post-partum haemorrhage

Table 2.6: Indications for VTE prophylaxis and duration of therapy

Prophylactic treatment

- Low molecular weight heparin, e.g.
- Enoxaparin, SC:
  - Body weight <100 kg: 40 mg daily. *LoE:IIb*[xlii]
  - Body weight ≥100 kg: 60 mg daily.
  - For post-partum prophylaxis, start 6–12 hours after delivery.

LoE:IIIb[xliii]

Note:

- Although LMWH related skin reactions are generally rare, they are more common in pregnant women. Monitor injection site for potential skin reactions.
- Women receiving antenatal LMWH should be advised that if they have any vaginal bleeding or once labour begins they should not inject any further LMWH.
- Spinal or epidural anaesthesia should be avoided if possible until at least 12 hours after the previous prophylactic dose of LMWH.
- The use of warfarin for VTE prophylaxis and treatment during pregnancy is not recommended, except in the setting of valvular disease and atrial fibrillation (see Section 6.3: Heart disease in pregnancy).
- Women that were either 1) on long-term anticoagulation with warfarin before pregnancy, or 2) require anticoagulation for 6 weeks post delivery can be converted from LMWH to warfarin postpartum when the risk of haemorrhage is reduced, usually 5–7 days after delivery.

LoE:IIIb[xliv]

- Initiation of warfarin will require continued anticoagulation with LMWH at prophylactic doses (see above) until the INR is within the therapeutic range:
  - Warfarin, oral, 5 mg daily.
  - INR should be done after 48 hours, then every 1 to 2 days until the INR is within the therapeutic range of 2-3 (refer to initiation dosing tables in the Appendix II).
  - Adjust dose to keep INR within therapeutic range (refer to maintenance dosing tables in the Appendix II).
  - Monitor INR at week 1, 2, and 4 (more frequent monitoring may be required if INR is out of therapeutic range).
  - All women of reproductive age should be on appropriate contraception (see chapter PHC STGs and EML, chapter 7: Family Planning). If a pregnancy is planned, do frequent pregnancy tests and change to LMWH once pregnancy is confirmed.
  - For all major elective surgery and other elective procedures with a significant bleeding risk, such as neuraxial anaesthesia and lumbar
  - punctures, the INR should be <1.5.
  - Educate patient on signs and symptoms of warfarin toxicity, and on risks associated with drastic dietary changes such as increased consumption of cruciferous vegetables.
- Warfarin is safe in breastfeeding.

Acute treatment of VTE or pulmonary embolism: *LoE:IIIb*[xlv]

- Low molecular weight heparin, e.g.: *LoE:IIIb*[xlvi]
- Enoxaparin SC, 1 mg/kg every 12 hours.
  - Discontinue treatment at least 24 hours prior to delivery, if the delivery time is predictable.
  - Continue treatment for 6 weeks post partum, and for at least three months in total.

REFERRAL/CONSULTATION DURING PREGNANCY

» Heparin-induced thrombocytopenia.
» Heritable or acquired thrombophilia.
» Medical comorbidities for consultation with specialist: heart or lung disease, SLE, cancer, inflammatory conditions, nephrotic syndrome, sickle cell disease, anti-phospholipid syndrome.

References:

[i] Ferrous sulfate/fumarate, oral: Reveiz L, Gyte GM, Cuervo LG, Casasbuenas A. Treatments for iron-deficiency anaemia in pregnancy. Cochrane Database Syst Rev. 2011 Oct 5;(10):CD003094. https://www.ncbi.nlm.nih.gov/pubmed/21975735

Ferrous sulfate/fumarate, oral : Rimon E, Kagansky N, Kagansky M, Mechnick L, Mashiah T, Namir M, Levy S. Are we giving too much iron? Low-dose iron therapy is effective in octogenarians. Am J Med. 2005 Oct;118(10):1142-7. https://www.ncbi.nlm.nih.gov/pubmed/16194646

Ferrous sulfate/fumarate, oral (duration of therapy): Alleyne M, Horne MK, Miller JL. Individualized treatment for iron-deficiency anemia in adults. Am J Med. 2008 Nov;121(11):943-8. http://www.ncbi.nlm.nih.gov/pubmed/18954837

Ferrous sulfate/fumarate, oral: South African Medicines Formulary. 14th Edition. Division of Clinical Pharmacology. University of Cape Town, 2022.

[ii] Ferrous sulfate/fumarate, oral (alternate day dosing – treatment of anaemia): Moretti D, Goede JS, Zeder C, Jiskra M, Chatzinakou V, Tjalsma H, Melse-Boonstra A, Brittenham G, Swinkels DW, Zimmermann MB. Oral iron supplements increase hepcidin and decrease iron absorption from daily or twice-daily doses in iron-depleted young women. Blood. 2015 Oct 22;126(17):1981-9. https://www.ncbi.nlm.nih.gov/pubmed/26289639

Ferrous sulfate/fumarate, oral (alternate day dosing – treatment of anaemia: Stoffel NU, Cercamondi CI, Brittenham G, Zeder C, Geurts-Moespot AJ, Swinkels DW, Moretti D, Zimmermann MB. Iron absorption from oral iron supplements given on consecutive versus alternate days and as single morning doses versus twice-daily split dosing in iron-depleted women: two open-label, randomised controlled trials. Lancet Haematol. 2017 Nov;4(11):e524-e533. https://www.ncbi.nlm.nih.gov/pubmed/29032957

[iii] Parenteral iron (hypotensive side-effect): South African Medicines Formulary. 14th Edition. Division of Clinical Pharmacology. University of Cape Town, 2022.

[iv] Parenteral iron (directions for use): South African Medicines Formulary. 14th Edition. Division of Clinical Pharmacology. University of Cape Town, 2022.

[v] Low molecular weight iron dextran: Atalay H, Solak Y, Acar K, Govec N, Turk S. Safety profiles of total dose infusion of low-molecular-weight iron dextran and high-dose iron sucrose in renal patients. Hemodial Int. 2011 Jul;15(3):374-8. http://www.ncbi.nlm.nih.gov/pubmed/21564503

Low molecular weight iron dextran: Solak Y, Atalay H, Guney I, Turkmen K, Kaya E, Turk S. Comparison of adverse-event profiles of intravenous low-molecular-weight iron dextran and iron sucrose in peritoneal dialysis patients. Ren Fail. 2011;33(3):307-11. http://www.ncbi.nlm.nih.gov/pubmed/21401355

[vi] Iron prophylaxis (pregnancy): Tunkyi K, Moodley J. Prevalence of anaemia in pregnancy in a regional health facility in South Africa. S Afr Med J. 2015;106(1):101-4. https://www.ncbi.nlm.nih.gov/pubmed/26792317

[vii] Iron prophylaxis (pregnancy): National Department of Health: Affordable Medicines, EDP-Primary Health Care level. Medicine Review: Intermittent iron supplementation in pregnancy: 6 November 2017. https://www.knowledgehub.org.za/content/standard-treatment-guidelines-and-essential-medicines-list

Iron prophylaxis (pregnancy): Pena-Rosas JP, De-Regil LM, Gomez Malave H, Flores-Urrutia MC, Dowswell T. Intermittent oral iron supplementation during pregnancy. The Cochrane database of systematic reviews. 2015(10):CD009997. https://www.ncbi.nlm.nih.gov/pubmed/26482110

[viii] Vitamin B_{12}, IM (dosing for uncomplicated pernicious anaemia): South African Medicines Formulary. 14th Edition. Division of Clinical Pharmacology. University of Cape Town, 2022.

Vitamin B_{12}, IM (dosing for uncomplicated pernicious anaemia): Joint Formulary Committee. British National Formulary. 80. London: BMJ Group and Pharmaceutical Press; 2020.

[ix] Prednisone: Neunert C, Lim W, Crowther M, Cohen A, Solberg L Jr, Crowther MA; American Society of Hematology. The American Society of Hematology 2011 evidence-based practice guideline for immune thrombocytopenia. Blood. 2011 Apr 21;117(16):4190-207. http://www.ncbi.nlm.nih.gov/pubmed/21325604

[x] Immunosuppresive therapy (e.g. Azathioprine): Hitzig WH, Massimo L. Treatment of autoimmune hemolytic anemia in children with azathioprine (imuran). Blood. 1966 Dec;28(6):840-50. http://www.ncbi.nlm.nih.gov/pubmed/5959475

Immunosuppresive therapy (e.g. Azathioprine): Worlledge SM, Brain MC, Cooper AC, Hobbs JR, Dacie JV. Immmunosuppressive drugs in the treatment of autoimmune haemolytic anaemia. Proc R Soc Med. 1968 Dec 12;61(12):1312-5. http://www.ncbi.nlm.nih.gov/pubmed/4177973

[xi] Heparin, SC: Collins R, Scrimgeour A, Yusuf S, Peto R. Reduction in fatal pulmonary embolism and venous thrombosis by perioperative administration of subcutaneous heparin. Overview of results of randomized trials in general, orthopedic, and urologic surgery. N Engl J Med. 1988 May 5;318(18):1162-73. https://www.ncbi.nlm.nih.gov/pubmed/3283548

Low molecular weight heparin (first line option - treatment): National Department of Health: Affordable Medicines, EDP-Adult Hospital Level. Cost-effectiveness and budget impact analyses: Fondaparinux for the treatment of venous thromboembolism in hospitalised patients in the South African public health system, April 2018. https://www.knowledgehub.org.za/content/standard-treatment-guidelines-and-essential-medicines-list

[xii] Low molecular weight heparin (morbid obesity): Lalama JT, Feeney ME, Vandiver JW, Beavers KD, Walter LN, McClintic JR. Assessing an enoxaparin dosing protocol in morbidly obese patients. J Thromb Thrombolysis. 2015 May;39(4):516-21. http://www.ncbi.nlm.nih.gov/pubmed/25087072

Low molecular weight heparin (morbid obesity): Spinler SA, Inverso SM, Cohen M, Goodman SG, Stringer KA, Antman EM; ESSENCE and TIMI 11B Investigators. Safety and efficacy of unfractionated heparin versus enoxaparin in patients who are obese and patients with severe renal impairment: analysis from the ESSENCE and TIMI 11B studies. Am Heart J. 2003 Jul;146(1):33-41. http://www.ncbi.nlm.nih.gov/pubmed/12851605

Low molecular weight heparin (morbid obesity): Thompson-Moore NR, Wanat MA, Putney DR, Liebl PH, Chandler WL, Muntz JE. Evaluation and Pharmacokinetics of Treatment Dose Enoxaparin in Hospitalized Patients With Morbid Obesity. Clin Appl Thromb Hemost. 2015 Sep;21(6):513-20. http://www.ncbi.nlm.nih.gov/pubmed/25601898

Low molecular weight heparin (morbid obesity): Freeman A, Horner T, Pendleton RC, Rondina MT. Prospective comparison of three enoxaparin dosing regimens to achieve target anti-factor Xa levels in hospitalized, medically ill patients with extreme obesity. Am J Hematol. 2012 Jul;87(7):740-3. http://www.ncbi.nlm.nih.gov/pubmed/22565589

[xiii] Low molecular weight heparin (renal impairment): South African Medicines Formulary. 14th Edition. Division of Clinical Pharmacology. University of Cape Town, 2022.

[xiv] Neutropaenia – urgent empiric management: Wein L, Wein S, Haas SJ, Shaw J, Krum H. Freifeld AG, Bow EJ, Sepkowitz KA, Boeckh MJ, Ito JI, Mullen CA, Raad II, Rolston KV, Young JA, Wingard JR; Infectious Diseases Society of Americaa. Clinical practice guideline for the use of antimicrobial agents in neutropenic patients with cancer: 2010 Update by the Infectious Diseases Society of America. Clin Infect Dis. 2011 Feb 15;52(4):427-31. https://www.ncbi.nlm.nih.gov/pubmed/21205990

Neutropaenia – urgent empiric management: National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology. Prevention and treatment of cancer-related infections, 2018 http://www.nccn.org

[xv] Piperacillin/taxobactam dose: Stanford Hospital and Clinics (SHC). SHC-Extended-Infusion-Piperacillin-Tazobactam.pdf (stanford.edu)

Package Insert – Tazocin. Pfizer Laboratories (Pty) Ltd. 02 May 2002.

[xvi] Piperacillin/taxobactam and amikacin: Nau R, Kinzig-Schippers M, Sörgel F, Schinschke S, Rössing R, Müller C, Kolenda H, Prange HW. Kinetics of piperacillin and tazobactam in ventricular cerebrospinal fluid of hydrocephalic patients.Antimicrob Agents Chemother. 1997 May;41(5):987-91.http://www.ncbi.nlm.nih.gov/pubmed/9145857

Piperacillin/taxobactam and amikacin: NICD AMR surveillance for ESKAPE, 1 January 2016 to 31 December 2016.

[xvii] Cefipime, IV (2 g): NICD AMR surveillance for ESKAPE, 1 January 2016 to 31 December 2016.

Cefipime, IV (2 g): South African Medicines Formulary. 14th Edition. Division of Clinical Pharmacology. University of Cape Town. 2022.

[xviii] G C White 2nd, Rosendaal F, Aledort LM, Lusher JM, Rothschild C, Ingerslev J0; Factor VIII and Factor IX Subcommittee. Definitions in hemophilia. Recommendation of the scientific subcommittee on factor VIII and factor IX of the scientific and standardization committee of the International Society on Thrombosis and Haemostasis. Thromb Haemost. 2001 Mar;85(3):560.

[xix] Lyophilised plasma: Bindi ML, Miccoli M, Marietta M, Meacci L, Esposito M, Bisà M, Mozzo R, Mazzoni A, Baggiani A, Scatena F, Filipponi F, Biancofiore G. Solvent detergent vs. fresh frozen plasma in cirrhotic patients undergoing liver transplant surgery: a prospective randomized control study. Vox Sang. 2013 Aug;105(2):137-43. http://www.ncbi.nlm.nih.gov/pubmed/23448618

Lyophilised plasma: Lerner RG, Nelson J, Sorcia E, Grima K, Kancherla RR, Zarou-Naimo CM, Pehta JC. Evaluation of solvent/detergent-treated plasma in patients with a prolonged prothrombin time. Vox Sang. 2000;79(3):161-7. http://www.ncbi.nlm.nih.gov/pubmed/11111235

Lyophilised plasma: Williamson LM, Llewelyn CA, Fisher NC, Allain JP, Bellamy MC, Baglin TP, Freeman J, Klinck JR, Ala FA, Smith N, Neuberger J, Wreghitt TG. A randomized trial of solvent/detergent-treated and standard fresh-frozen plasma in the coagulopathy of liver disease and liver transplantation. Transfusion. 1999 Nov-Dec;39(11-12):1227-34. http://www.ncbi.nlm.nih.gov/pubmed/10604250

Lyophilised plasma: Huisman EL, de Silva SU, de Peuter MA. Economic evaluation of pooled solvent/detergent treated plasma versus single donor fresh-frozen plasma in patients receiving plasma transfusions in the United States. Transfus Apher Sci. 2014 Aug;51(1):17-24. http://www.ncbi.nlm.nih.gov/pubmed/25151097

Lyophilised plasma: National Department of Health: Affordable Medicines, EDP-Adult Hospital Level. Price comparison analysis, updated: Fresh frozen plasma vs lyophilised plasma, September 2019. https://www.knowledgehub.org.za/content/standard-treatment-guidelines-and-essential-medicines-list

[xx] Factor VIII: World Federation of Haemophilia. 2012. Guidelines for Management of Haemophilia. http://www1.wfh.org/publication/files/pdf-1472.pdf

Factor VIII: Mahlangu JN, Gilham A. Guideline for the Treatment of Haemophilia in South Africa. S Afr Med J 2008; 98: 125-140. http://www.samj.org.za/index.php/samj/article/view/336/723

[xxi] Factor IX: World Federation of Haemophilia. 2012. Guidelines for Management of Haemophilia. http://www1.wfh.org/publication/files/pdf-1472.pdf

Factor IX: Mahlangu JN, Gilham A. Guideline for the Treatment of Haemophilia in South Africa. S Afr Med J 2008; 98: 125-140. http://www.samj.org.za/index.php/samj/article/view/336/723

[xxii] Prednisone, oral: Provan D, Stasi R, Newland AC, Blanchette VS, Bolton-Maggs P, Bussel JB, Chong BH, Cines DB, Gernsheimer TB, Godeau B, Grainger J, Greer I, Hunt BJ, Imbach PA, Lyons G, McMillan R, Rodeghiero F, Sanz MA, Tarantino M, Watson S, Young J, Kuter DJ. International consensus report on the investigation and management of primary immune thrombocytopenia. Blood. 2010 Jan 14;115(2):168-86. https://www.ncbi.nlm.nih.gov/pubmed/9846889

Prednisone, oral: Neunert C, Lim W, Crowther M, Cohen A, Solberg L Jr, Crowther MA; American Society of Hematology. The American Society of Hematology 2011 evidence-based practice guideline for immune thrombocytopenia. Blood. 2011 Apr 21;117(16):4190-207. https://www.ncbi.nlm.nih.gov/pubmed/21325604

[xxiii] Methylprednisolone, IV: Alpdogan O, Budak-Alpdogan T, Ratip S, Firatli-Tuglular T, Tanriverdi S, Karti S, Bayik M, Akoglu T. Efficacy of high-dose methylprednisolone as a first-line therapy in adult patients with idiopathic thrombocytopenic purpura. Br J Haematol. 1998 Dec;103(4):1061-3. http://www.ncbi.nlm.nih.gov/pubmed/9886319

[xxiv] Lyophilised plasma: Bindi ML, Miccoli M, Marietta M, Meacci L, Esposito M, Bisà M, Mozzo R, Mazzoni A, Baggiani A, Scatena F, Filipponi F, Biancofiore G. Solvent detergent vs. fresh frozen plasma in cirrhotic patients undergoing liver transplant surgery: a prospective randomized control study. Vox Sang. 2013 Aug;105(2):137-43. http://www.ncbi.nlm.nih.gov/pubmed/23448618

Lyophilised plasma: Lerner RG, Nelson J, Sorcia E, Grima K, Kancherla RR, Zarou-Naimo CM, Pehta JC. Evaluation of solvent/detergent-treated plasma in patients with a prolonged prothrombin time. Vox Sang. 2000;79(3):161-7. http://www.ncbi.nlm.nih.gov/pubmed/11111235

Lyophilised plasma: Williamson LM, Llewelyn CA, Fisher NC, Allain JP, Bellamy MC, Baglin TP, Freeman J, Klinck JR,

Ala FA, Smith N, Neuberger J, Wreghitt TG. A randomized trial of solvent/detergent-treated and standard fresh-frozen plasma in the coagulopathy of liver disease and liver transplantation. Transfusion. 1999 Nov-Dec;39(11-12):1227-34. http://www.ncbi.nlm.nih.gov/pubmed/10604250

Lyophilised plasma: Huisman EL, de Silva SU, de Peuter MA. Economic evaluation of pooled solvent/detergent treated plasma versus single donor fresh-frozen plasma in patients receiving plasma transfusions in the United States. Transfus Apher Sci. 2014 Aug;51(1):17-24. http://www.ncbi.nlm.nih.gov/pubmed/25151097

Lyophilised plasma: National Department of Health: Affordable Medicines, EDP-Adult Hospital Level. Price comparison analysis, updated: Fresh frozen plasma vs lyophilised plasma, September 2019. https://www.knowledgehub.org.za/content/standard-treatment-guidelines-and-essential-medicines-list

[xxv] Lyophilised plasma: Bindi ML, Miccoli M, Marietta M, Meacci L, Esposito M, Bisà M, Mozzo R, Mazzoni A, Baggiani A, Scatena F, Filipponi F, Biancofiore G. Solvent detergent vs. fresh frozen plasma in cirrhotic patients undergoing liver transplant surgery: a prospective randomized control study. Vox Sang. 2013 Aug;105(2):137-43. http://www.ncbi.nlm.nih.gov/pubmed/23448618

Lyophilised plasma: Lerner RG, Nelson J, Sorcia E, Grima K, Kancherla RR, Zarou-Naimo CM, Pehta JC. Evaluation of solvent/detergent-treated plasma in patients with a prolonged prothrombin time. Vox Sang. 2000;79(3):161-7. http://www.ncbi.nlm.nih.gov/pubmed/11111235

Lyophilised plasma: Williamson LM, Llewelyn CA, Fisher NC, Allain JP, Bellamy MC, Baglin TP, Freeman J, Klinck JR, Ala FA, Smith N, Neuberger J, Wreghitt TG. A randomized trial of solvent/detergent-treated and standard fresh-frozen plasma in the coagulopathy of liver disease and liver transplantation. Transfusion. 1999 Nov-Dec;39(11-12):1227-34. http://www.ncbi.nlm.nih.gov/pubmed/10604250

Lyophilised plasma: Huisman EL, de Silva SU, de Peuter MA. Economic evaluation of pooled solvent/detergent treated plasma versus single donor fresh-frozen plasma in patients receiving plasma transfusions in the United States. Transfus Apher Sci. 2014 Aug;51(1):17-24. http://www.ncbi.nlm.nih.gov/pubmed/25151097

Lyophilised plasma: National Department of Health: Affordable Medicines, EDP-Adult Hospital Level. Price comparison analysis, updated: Fresh frozen plasma vs lyophilised plasma, September 2019. https://www.knowledgehub.org.za/content/standard-treatment-guidelines-and-essential-medicines-listhttp://www.health.gov.za/

[xxvi] Non-pharmacological management – VTE prophylaxis: Goldhaber SZ, Turpie AG. Prevention of venous thromboembolism among hospitalized medical patients. Circulation. 2005 Jan 4;111(1):e1-3. https://www.ncbi.nlm.nih.gov/pubmed/15630031

[xxvii] NDoH review. DOACS for prevention of VTE. V6.0_12 October 2023

[xxviii] Low molecular weight heparin (enoxaparin dosing in renal impairment): South African Medicines Formulary. 14th Edition. Division of Clinical Pharmacology. University of Cape Town, 2022.

[xxix] Heparin, SC: Collins R, Scrimgeour A, Yusuf S, Peto R. Reduction in fatal pulmonary embolism and venous thrombosis by perioperative administration of subcutaneous heparin. Overview of results of randomized trials in general, orthopedic, and urologic surgery. N Engl J Med. 1988 May 5;318(18):1162-73. https://www.ncbi.nlm.nih.gov/pubmed/3283548

Heparin, SC (dosing in renal impairment): South African Medicines Formulary. 14th Edition. Division of Clinical Pharmacology. University of Cape Town, 2022.

[xxx] NDoH review. Aspirin for VTE prophylaxis. V1.0_12 October 2023

[xxxi] NDoH review. DOACS for prevention of VTE. V6.0_12 October 2023

NDoH. Adaptation of NICE Guidance 30 November 2023

[xxxii] Low molecular weight heparin (enoxaparin dosing in renal impairment): South African Medicines Formulary. 14th Edition. Division of Clinical Pharmacology. University of Cape Town, 2022.

[xxxiii] Heparin, SC: Collins R, Scrimgeour A, Yusuf S, Peto R. Reduction in fatal pulmonary embolism and venous thrombosis by perioperative administration of subcutaneous heparin. Overview of results of randomized trials in general, orthopedic, and urologic surgery. N Engl J Med. 1988 May 5;318(18):1162-73. https://www.ncbi.nlm.nih.gov/pubmed/3283548

Heparin, SC (dosing in renal impairment): South African Medicines Formulary. 14th Edition. Division of Clinical Pharmacology. University of Cape Town, 2022.

[xxxiv] DOACS (treatment of VTE): National Department of Health: Affordable Medicines, EDP-Adult Hospital Level. Medicine Review. DOACs: Treatment of DVT&PE_Adults_v6.0_30 November 2023.

[xxxv] Low molecular weight heparin (first line option - treatment): National Department of Health: Affordable Medicines, EDP-Adult Hospital Level. Medicine Review LMWH vs. UFH for the prophylaxis and treatment of venous thromboembolism and acute coronary syndromes, April 2018. http://www.health.gov.za/

Low molecular weight heparin (first line option - treatment): Junqueira DR, Zorzela LM, Perini E. Unfractionated heparin versus low molecular weight heparins for avoiding heparin-induced thrombocytopenia in postoperative patients. Cochrane Database Syst Rev. 2017 Apr 21;4:CD007557. https://www.ncbi.nlm.nih.gov/pubmed/28431186

Low molecular weight heparin (first line option - treatment): Wein L, Wein S, Haas SJ, Shaw J, Krum H. Pharmacological venous thromboembolism prophylaxis in hospitalized medical patients: a meta-analysis of randomized controlled trials. Arch Intern Med. 2007 Jul 23;167(14):1476-86. https://www.ncbi.nlm.nih.gov/pubmed/17646601

Low molecular weight heparin (first line option - treatment): National Department of Health: Affordable Medicines, EDP-Adult Hospital Level. Cost-effectiveness and budget impact analyses: Fondaparinux for prophylaxis of venous thromboembolism in medical and surgical patients in hospitalised patients in the South African public health system, April 2018. http://www.health.gov.za/

[xxxvi] Enoxaparin, SC (dosing for treatment of VTE): National Department of Health: Affordable Medicines, EDP-Adult Hospital Level. Medicine Review LMWH vs. UFH for the prophylaxis and treatment of venous thromboembolism and acute coronary syndromes – Appendix A, April 2018. http://www.health.gov.za/

Low molecular weight heparin (dosing for treatment of VTE): Bhutia S, Wong PF. Once versus twice daily low molecular

weight heparin for the initial treatment of venous thromboembolism. Cochrane database Syst Rev. 2013 Jul;(7):CD003074. https://www.ncbi.nlm.nih.gov/pubmed/23857562

[xxxvii] Low molecular weight heparin (morbid obesity): Lalama JT, Feeney ME, Vandiver JW, Beavers KD, Walter LN, McClintic JR. Assessing an enoxaparin dosing protocol in morbidly obese patients. J Thromb Thrombolysis. 2015 May;39(4):516-21. http://www.ncbi.nlm.nih.gov/pubmed/25087072

Low molecular weight heparin (morbid obesity): Spinler SA, Inverso SM, Cohen M, Goodman SG, Stringer KA, Antman EM; ESSENCE and TIMI 11B Investigators. Safety and efficacy of unfractionated heparin versus enoxaparin in patients who are obese and patients with severe renal impairment: analysis from the ESSENCE and TIMI 11B studies. Am Heart J. 2003 Jul;146(1):33-41. http://www.ncbi.nlm.nih.gov/pubmed/12851605

Low molecular weight heparin (morbid obesity): Thompson-Moore NR, Wanat MA, Putney DR, Liebl PH, Chandler WL, Muntz JE. Evaluation and Pharmacokinetics of Treatment Dose Enoxaparin in Hospitalized Patients With Morbid Obesity. Clin Appl Thromb Hemost. 2015 Sep;21(6):513-20. http://www.ncbi.nlm.nih.gov/pubmed/25601898

Low molecular weight heparin (morbid obesity): Freeman A, Horner T, Pendleton RC, Rondina MT. Prospective comparison of three enoxaparin dosing regimens to achieve target anti-factor Xa levels in hospitalized, medically ill patients with extreme obesity. Am J Hematol. 2012 Jul;87(7):740-3. http://www.ncbi.nlm.nih.gov/pubmed/22565589

[xxxviii] Low molecular weight heparin (renal impairment): South African Medicines Formulary. 12th Edition. Division of Clinical Pharmacology. University of Cape Town, 2016.

[xxxix] Warfarin, oral (directions for use): South African Medicines Formulary. 14th Edition. Division of Clinical Pharmacology. University of Cape Town, 2022.

[xl] Thrombosis and Embolism during Pregnancy and the Puerperium: Acute Management (Green-top Guideline No. 37b) [Internet]. RCOG. [cited 2022 Nov 1]. Available from: https://www.rcog.org.uk/guidance/browse-all-guidance/green-top-guidelines/thrombosis-and-embolism-during-pregnancy-and-the-puerperium-acute-management-green-top-guideline-no-37b/

[xli] VTE LMWH prophylaxis (pregnancy): Bates SM, Greer IA, Middeldorp S, Veenstra DL, Prabulos AM, Vandvik PO. VTE, Thrombophilia, Antithrombotic Therapy, and Pregnancy: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest. 2012 Feb 1;141(2, Supplement):e691S-e736S. https://pubmed.ncbi.nlm.nih.gov/22315276/

[xlii] VTE LMWH prophylaxis – fixed doses (pregnancy): Bistervels IM, Buchmüller A, Wiegers HMG, Ní Áinle F, Tardy B, Donnelly J, et al; Highlow Block writing committee; Highlow Investigators. Intermediate-dose versus low-dose low-molecular-weight heparin in pregnant and post-partum women with a history of venous thromboembolism (Highlow study): an open-label, multicentre, randomised, controlled trial. Lancet. 2022 Oct 28:S0140-6736(22)02128-6. https://pubmed.ncbi.nlm.nih.gov/36354038/

[xliii] Enoxaparin (skin reactions): Schindewolf M, Lindhoff-Last E, Ludwig RJ, Boehncke WH. Heparin-induced skin lesions. Lancet. 2012 Nov 24;380(9856):1867-79. doi: 10.1016/S0140-6736(12)60409-7. Epub 2012 May 28. PMID: 22642893.

Schindewolf M, Gobst C, Kroll H, et al. Pregnant women have an increased risk for heparin-induced allergic skin reactions—results of a prospective investigation. Vasa 2010; 39: 61–62 (abstract).

[xliv] VTE LMWH prophylaxis – fixed doses (pregnancy): Bistervels IM, Buchmüller A, Wiegers HMG, Ní Áinle F, Tardy B, Donnelly J, et al; Highlow Block writing committee; Highlow Investigators. Intermediate-dose versus low-dose low-molecular-weight heparin in pregnant and post-partum women with a history of venous thromboembolism (Highlow study): an open-label, multicentre, randomised, controlled trial. Lancet. 2022 Oct 28:S0140-6736(22)02128-6. https://pubmed.ncbi.nlm.nih.gov/36354038/

Management of DVT prophylaxis in pregnancy: National Department of Health: Affordable Medicines, EDP-Adult Hospital Level. Evidence Summary: LMWH for VTE prophylaxis during pregnancy, November 2022. https://www.knowledgehub.org.za/content/standard-treatment-guidelines-and-essential-medicines-list

[xlv] Enoxaparin, SC (dosing for treatment of VTE): National Department of Health: Affordable Medicines, EDP-Adult Hospital Level. Medicine Review LMWH vs. UFH for the prophylaxis and treatment of venous thromboembolism and acute coronary syndromes – Appendix A, April 2018. https://www.knowledgehub.org.za/content/standard-treatment-guidelines-and-essential-medicines-list

Low molecular weight heparin (dosing for treatment of VTE): Bhutia S, Wong PF. Once versus twice daily low molecular weight heparin for the initial treatment of venous thromboembolism. Cochrane database Syst Rev. 2013 Jul;(7):CD003074. https://www.ncbi.nlm.nih.gov/pubmed/23857562

[xlvi]VTE LMWH acute treatment (pregnancy): Bates SM, Greer IA, Middeldorp S, Veenstra DL, Prabulos AM, Vandvik PO. VTE, Thrombophilia, Antithrombotic Therapy, and Pregnancy: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest. 2012 Feb 1;141(2, Supplement):e691S-e736S. https://pubmed.ncbi.nlm.nih.gov/22315276/

CHAPTER 3
CARDIOVASCULAR SYSTEM

3.1 ISCHAEMIC HEART DISEASE AND ATHEROSCLEROSIS, PREVENTION

Major risk factors for ischaemic cardio- and cerebrovascular disease:
» Diabetes mellitus.
» Hypertension.
» Central obesity (waist circumference): men ≥102 cm, women ≥88 cm.
» Smoking.
» Dyslipidaemia:
  - Total cholesterol >5.0 mmol/L, or
  - LDL >3 mmol/L, or
  - HDL <1 mmol/L in men and <1.2 mmol/L in women.
» Family history of premature cardiovascular disease in first degree male relatives <55 years and in first degree female relatives <65 years.
» Age: men >55 years, women >65 years.

LoE:IIIb[i]

» Psychological stress.

GENERAL MEASURES

Lifestyle modification, especially smoking cessation, is essential and often has greater beneficial impact on prognosis than vascular interventions and medications.

All persons should be encouraged to make the following lifestyle changes as appropriate (consult dietitian, if available):

LoE:IIIb[ii]

» Smoking cessation.
» Weight reduction in overweight patients, i.e. maintain BMI 18.5 to 25 kg/m^2.
» Reduce alcohol intake to no more than 2 standard drinks/day for males and 1 for females. (1 standard drink = a can of beer = a glass of wine = a shot of spirits.)
» Follow a prudent eating plan i.e. low saturated fat, high fibre and unrefined carbohydrates, with adequate fresh fruit and vegetables.
» Moderate aerobic exercise, e.g. 30 minutes brisk walking 5-7 times/week (150 minutes/week).

MEDICINE TREATMENT

Indications for lipid lowering medicine therapy

Patients with any of the following factors are at a relatively high risk for a cardiovascular event and should receive lipid lowering therapy:

» Established atherosclerotic disease:

  - ischaemic heart disease,
  - peripheral vascular disease,
  - atherothrombotic stroke.

» Type 2 diabetes with age >40 years.

LoE:IIa[iii]

» Diabetes for >10 years.
» Diabetes with chronic kidney disease (eGFR <60 mL/minute).

Patients with any of the following factors are also potentially at risk for cardiovascular disease (other than the categories above):

» diabetes mellitus,
» hypertension,
» central obesity: waist circumference ≥94 cm (men) and ≥80 cm (women),
» smoking,

LoE:IIIb[iv]

» age: men >55 years of age, women >65 years of age,
» psychological stress.

These patients should be managed according to their 10–year risk of a cardiovascular event as calculated using either:

A. BMI–based risk assessment, or
B. Framingham risk score (cholesterol-based assessment). See Appendix VII Cardiovascular risk assessment.

Management is based on the patient's 10-year risk of a cardiovascular event:

- <10% risk: lifestyle modification and risk assess patient every 5 years.
- 10–20% risk: lifestyle modification and risk assess patient annually.
- ≥20% risk: lifestyle modification and start statin treatment.

Note:

» Lipid lowering medicines should be given to those with a high risk of CVD even if cholesterol is within the desirable range.

▪ HMGCoA reductase inhibitors (statins), according to table below:

INDICATION	HMGCOA REDUCTASE INHIBITOR (STATIN) DOSE
A: Primary prevention - no existing CVD	
» Type 2 diabetes with age >40 years. » Diabetes for >10 years. » Diabetes with chronic kidney disease. » ≥ 20% 10-year risk of cardiovascular event.	▪ HMGCoA reductase inhibitors (statins), e.g.: • Simvastatin, oral, 10 mg at night.
» Patients on protease inhibitors. (Risks as above, after switching to atazanavir – see section below).	• Atorvastatin, oral, 10 mg daily.

B: Secondary prevention - existing CVD	
» Ischaemic heart disease. » Atherothrombotic stroke. » Peripheral vascular disease.	▪ HMGCoA reductase inhibitors (statins), e.g.: • Rosuvastatin, oral, 10 mg at night. LoE:Ia[v]
» Patients on protease inhibitors.	• Atorvastatin, oral, 10 mg daily. LoE:Ia[vi]
» Patients on amlodipine (and not on protease inhibitor).	• Simvastatin, oral, 10–20 mg at night. LoE:IIIb[vii]
» If patient complains of muscle pain.	Reduce dose: ▪ HMGCoA reductase inhibitors (statins), e.g.: • Simvastatin, oral, 10 mg at night. **OR** Consult specialist for further management. LoE:IIIb[viii]

Table 3.1: Management with HMGCoA reductase inhibitors
Note: Lipid-lowering medicines must always be used in conjunction with ongoing lifestyle modification.

Protease inhibitor-induced dyslipidaemia:

» Certain antiretroviral medication, particularly protease inhibitors, can cause dyslipidaemia. Fasting lipid levels should be done 3 months after starting lopinavir/ritonavir. Lopinavir/ritonavir is associated with a higher risk of dyslipidaemia (specifically hypertriglyceridaemia) than atazanavir/ritonavir.
» Patients at high risk (>20% risk of developing a CVD event in 10 years) should switch to atazanavir/ritonavir and repeat the fasting lipid profile in 3 months.
» Patients with persistent dyslipidaemia despite switching, qualify for lipid lowering therapy. Criteria for initiating lipid lowering therapy are the same as for HIV-negative patients. Many statins (including simvastatin) cannot be used with protease inhibitors, as protease inhibitors inhibit the metabolism of the statin resulting in extremely high blood levels.
» Patients at high risk for CVD who fail to respond to lifestyle modification and have dyslipidaemia on atazanavir/ritonavir treat with:

• Atorvastatin, oral, 10 mg at night.

REFERRAL

» Random cholesterol >7.5 mmol/L.
» Fasting (14 hours) triglycerides >10 mmol/L.

3.2 ACUTE CORONARY SYNDROMES

These conditions should be managed in a high care setting with continuous ECG and frequent BP monitoring.

Reference guide for ECG analysis: "ECG APPtitude" smartphone app can be downloaded from the relevant app stores - available for iOS and Android.

3.2.1 ST ELEVATION MYOCARDIAL INFARCTION (STEMI)

I21.0-I21.3/I21.9/I22.0-1/I22.8-9

DESCRIPTION

Ischaemic chest pain that is prolonged, ongoing or associated with nausea, sweating and syncope or associated with persistent ST elevation or new / presumed new left bundle branch block (LBBB). Repeat ECG at 20 to 30-minute intervals if the initial ECG is not diagnostic. Treatment should not be delayed while waiting for troponin results.

MEDICINE TREATMENT

LoE:IIb[ix]

Note: The following guidance is not for primary percutaneous coronary intervention (PCI).

- Oxygen if saturation <94%.

LoE:Ia[x]

- Clopidogrel, oral, 75 mg daily for one month.

AND

LoE:Ia[xi]

- Aspirin, oral, 150 mg immediately as a single dose (chewed

LoE:Ia[xii]

or dissolved).
  - Followed with 150 mg daily (continued indefinitely in absence of contraindications).

AND

Thrombolytic therapy

- Streptokinase, IV 1.5 million units diluted in 100 mL sodium chloride 0.9%, infused over 30–60 minutes. **Do not use heparin if streptokinase is given**.
  - Hypotension may occur. If it does, reduce the rate of infusion but strive to complete it in <60 minutes.
  - Streptokinase is antigenic and should not be re-administered in the

LoE:IIIb[xiii]

period of 5 days to 12 months after 1st administration.
  - Severe allergic reactions are uncommon but antibodies which may render it ineffective may persist for years.

Considerations for initiating thrombolytics	Contra-indications
» For acute myocardial infarction with ST elevation or left bundle branch block:	» Absolute: – streptokinase used within the last year, – previous allergy,

– maximal chest pain is ≤6 hours – if beyond 6 hours and ongoing chest pain – >6 hours and no chest pain, thrombolytic not indicated (see Section 3.2.2: NSTEMI) *LoE:Ia*[xiv]	– Confirmed CVA within the last 3 months, – history of recent major trauma, – bleeding within the last month, – aneurysms, – brain or spinal surgery or head injury within the preceding month, or recent (<3 weeks) major surgery, – active bleeding or known bleeding disorder, – aortic dissection. » <u>Relative (consult specialist):</u> – refractory hypertension, – warfarin therapy, – recent retinal laser treatment, – subclavian central venous catheter, – pregnancy, – TIA in the preceding 6 months, – traumatic resuscitation.

Table 3.2: Indications and contraindications for streptokinase

OR

<u>If streptokinase is unavailable:</u>

- Thrombolytic e.g.:

LoE:Ia[xv]

- Alteplase, IV infusion:
  - Do not exceed 100 mg.
  - If history of onset is less than 6 hours (beyond 6 hours consult a specialist or treat as NSTEMI (see below):

	Bolus	**Next 30 minutes**	**Next 60 minutes**
>65 kg	15 mg	50 mg	35 mg
≤65 kg	15 mg	0.75 mg/kg	0.5 mg/kg

LoE:IVb[xvi]

  - Indications and contraindications are similar to those for streptokinase as above (except that prior use of streptokinase is not a contra-indication).

Monitor the following, continuously and also during transfer:

» pulse
» BP
» respiration depth and rate (count for a full minute)
» ECG

Note: Defibrillator should be readily available at all times including during transport.

Adjunctive treatment

- Enoxaparin (after alteplase, do not use heparins after streptokinase).

- Loading dose: IV, 30 mg as a bolus, followed by SC, 1 mg/kg as a single dose (total cumulative dose not to exceed 100 mg).
- Maintenance dose: SC, 1.5 mg/kg daily or 1 mg/kg 12 hourly.
- Continue enoxaparin therapy until coronary angiography, or for the duration of hospitalisation to a maximum of 8 days.

LoE:IIb[xvii]

- In the elderly (>75 years of age), omit IV loading dose and reduce SC dose:

LoE:Ia[xviii]

  - Loading dose: SC, 0.75 mg/kg as a single dose.
  - Maintenance dose: SC, 1.5 mg/kg daily or 1 mg/kg 12 hourly.

Pain not responsive to thrombolytics may suggest ongoing unresolved ischaemia.
Discuss with specialist and consider the following treatments:

LoE:IIIb[xix]

- Nitrates, e.g.:
- Isosorbide dinitrate, SL, 5 mg immediately as a single dose.
  - May be repeated at 5-minute intervals for 3 or 4 doses.

For ongoing chest pain, to control hypertension or treat pulmonary oedema:

- Glyceryl trinitrate (GTN), IV, 5–200 mcg/minute, titrated to response.
  - Guidance on preparation and administration included below.

CAUTION
Glyceryl trinitrate IV formulation must be diluted before infusion.

STEP 1: Select the concentration as required for the individual patient
- For patients who are fluid congested or require higher doses for a clinical response, consider using a more concentrated solution e.g. 200 or 400 mcg/mL.

STEP 2: Select the volume of the diluent
- Patients who are likely to require treatment for a longer duration e.g. unstable angina prepare a larger volume e.g. 500mL.
- Compatible diluents include sodium chloride 0.9% or dextrose 5%.

STEP 3: Confirm the formulation of glyceryl trinitrate (GTN) available and mix with diluent
- Confirm the strength of the GTN solution i.e. whether a 1mg/mL or 5mg/mL formulation is available.
- Depending on the formulation available, select the number of ampoules to be used based on the concentration and volume of the diluent as decided in Step 1 and 2 above.

- Ensure that the equivalent volume of diluent is removed from the bag before adding the total GTN volume e.g. if 100mLs of GTN is to be added, first remove 100mL of diluent from the bag before adding the GTN.

STEP 4: Set the flow rate for infusion

- Flush the PVC tube before administering to patient.
- Start with the lowest flow rate possible based on the concentration of the solution prepared.
- Increase by 5 mcg/minute every 5 minutes until response achieved or until the rate is 20 mcg/minute.
- If no response after 20 mcg/minute increase by 20 mcg/minute until response.
- Monitor blood pressure carefully.

E.g. To prepare a 200mcg/mL solution for a patient likely to require several hours of the GTN infusion:
Use 10 ampoules (100mL) of the 1mg/mL GTN formulation mixed with 400mL of diluent (100mL to be removed from a 500mL bag). Initiate the infusion at a flow rate 3mL/hr and titrate the infusion rate based on the patient's response.

STEP 1	**STEP 2**	**STEP 3**			
Concentration of dilution	**Volume of diluent**	**Glyceryl trinitrate 1 mg/mL**		**Glyceryl trinitrate 5 mg/mL**	
		Volume (Dose)	Number of 10mL ampoules	Volume (Dose)	Number of 10mL ampoules
100 mcg/mL	250 mL	25 mL (25 mg)	2.5	5 mL (25 mg)	0.5
200 mcg/mL		50 mL (50 mg)	5	10 mL (50 mg)	1
400 mcg/mL		100 mL (100 mg)	10	20 mL (100 mg)	2
100 mcg/mL	500 mL	50 mL (50 mg)	5	10 mL (50 mg)	1
200 mcg/mL		100 mL (100 mg)	10	20 mL (100 mg)	2
400 mcg/mL		200 mL (200 mg)	20	40 mL (200 mg)	4

STEP 4	**Solution concentration (mcg/mL)**	**100 mcg/mL solution**	**200 mcg/mL solution**	**400 mcg/mL solution**
	Dose (mcg/min)	Flow rate (microdrops/min = mL/hr)		
	5	3	–	–
	10	6	3	–
	15	9	–	–
	20	12	6	3
	30	18	9	–
	40	24	12	6
	60	36	18	9
	80	48	24	12

	100	60	30	15
	120	72	36	18
	160	96	48	24
	200	–	60	30

Table 3.3: Dilution of glyceryl trinitrate

For severe pain unresponsive to nitrates:
Discuss with a specialist for possible transfer for rescue PCI, and then consider morphine:

- Morphine, IV, to a total maximum dose of 10 mg. (See Appendix II, for individual dosing and monitoring for response and toxicity.)
  - Ongoing severe pain despite all appropriate treatment above is an indication for urgent referral.

When clinically stable without signs of heart failure, hypotension, bradydysrhythmias or history of asthma:

- Cardio-selective β-blocker, e.g.:
- Atenolol, oral, 50 mg daily.

- HMGCoA reductase inhibitors (statins), e.g.:

LoE:Ia[xx]

- Rosuvastatin, oral, 10 mg at night.

LoEIa[xxi]

Patients on protease inhibitor:

- Atorvastatin, oral, 10 mg at night.

Patients on amlodipine (and not on a protease inhibitor):

LoE:IIIb[xxii]

- Simvastatin, oral, 10–20 mg at night.

If patient complains of muscle pain:
Reduce dose:

- HMGCoA reductase inhibitors (statins), e.g.:
- Simvastatin, oral, 10–20 mg at night.

OR

LoE:IIIb[xxiii]

Consult specialist for further management.

For left ventricular (LV) dysfunction following myocardial infarction, heart failure or ejection fraction <40%:

- ACE-inhibitor, e.g.:
- Enalapril, oral, target dose, 10 mg 12 hourly.

If ACE-inhibitor intolerant, i.e. intractable cough or angio-oedema:

- Angiotensin receptor blocker (ARB), e.g.:

- Losartan, oral, 50–100 mg daily. Specialist initiated.

» Angioedema is a potentially serious complication of ACE-inhibitor/ angiotensin receptor blocker treatment and if it occurs stop the medication and do not re-challenge.
» Concomitant use of fluoroquinolones with ACE-inhibitor/angiotensin receptor blocker is contraindicated in moderate to severe renal impairment (CrCl ≤30 mL/minute) and in the elderly. Assess renal function before initiating treatment and monitor during treatment.

LoE:IIIb[xxiv]

Institute other therapy for heart failure and LV dysfunction as described in Section 3.4: Congestive cardiac failure.

REFERRAL

» Refractory cardiogenic shock.
» Refractory pulmonary oedema.
» Haemodynamically compromising ventricular dysrhythmia.
» Patients with the combination of new right bundle and posterior fascicular block post MI should be referred for permanent pacemaker consideration as they are at high risk for progression to complete heart block.
» Myocardial infarction-related mitral regurgitation or ventricular septal defect (VSD).
» Contraindication to thrombolytic therapy provided a PCI facility available (confirm with cardiologist).
» Ongoing ischaemic chest pain.
» Failed reperfusion (<50% reduction in ST elevation at 90 minutes after initiation of streptokinase and 60 minutes after initiation of thrombolytics (e.g., alteplase) in leads showing greatest ST elevation, especially in anterior infarct or inferior infarct with right ventricular involvement).

3.2.2 NON-ST ELEVATION MYOCARDIAL INFARCTION (NSTEMI) AND UNSTABLE ANGINA (UA)

I21.4/I21.9/I20.0

DESCRIPTION

Non-ST elevation MI: Chest pain that is increasing in frequency and/or severity or occurring at rest. The chest pain is associated with elevated cardiac biomarkers and ST segment depression or T wave inversion on ECG, or a normal ECG. Biomarker elevation in the absence of diagnostic ECG changes or symptoms compatible with myocardial ischemia should prompt consideration of alternative diagnoses (e.g. heart failure, pulmonary embolism, chronic kidney disease, sepsis, myopericarditis). *LoE:IVb*[xxv]

Unstable angina pectoris: Chest pain that is increasing in frequency and or severity or occurring at rest. It also encompasses post-infarct angina. The chest pain may be associated with ST segment depression or T wave inversion on ECG. There is no rise in cardiac biomarkers.

MEDICINE TREATMENT

Note: The following guidance is not for primary percutaneous coronary intervention.

LoE:IIb[xxvi]

- Oxygen, if saturation <94%.

LoE:Ia[xxvii]

- Clopidogrel, oral, 300 mg.
  Followed by 75 mg daily for 3 months.

AND

LoE:Ia[xxviii]

- Aspirin, oral, 150 mg immediately as a single dose (chewed or dissolved).
  - Followed with 150 mg daily (continued indefinitely in absence of contraindications).

AND

Anticoagulation:

For NSTEMI and UA (also for STEMI not given thrombolytic therapy):

- Enoxaparin, SC, 1 mg/kg 12 hourly for minimum of 2 days.

OR

- Unfractionated heparin, IV bolus, 5 000 units.
  - Follow with 1 000–1 200 units hourly monitored by aPTT.

LoE:Ia[xxix]

  - Continue infusion for minimum of 2 days.

To relieve possible coronary spasm and pain and to reduce preload:

» Nitrates, e.g.:

- Isosorbide dinitrate SL, 5 mg immediately as a single dose.
  - May be repeated at 5-minute intervals for 3 or 4 doses.

For persistent pain and if oral therapy is insufficient:

- Glyceryl trinitrate, IV, 5–200 mcg/minute, titrated to response.
  - Start with 5 mcg/minute and increase by 5 mcg/minute every 5 minutes until response or until the rate is 20 mcg/minute.
  - If no response after 20 mcg/minute, increase by 20 mcg/minute every 5 minutes until pain reduction or medicine no longer tolerated.
  - Flush the PVC tube before administering the medicine to patient.
  - Monitor BP carefully.

For dilution of glyceryl trinitrate refer to Section 3.2.1: ST elevation myocardial infarction (STEMI).

For severe pain unresponsive to nitrates:
Discuss with a specialist for possible transfer for rescue PCI, and then consider morphine:

- Morphine, IV, to a total maximum dose of 10 mg (see Appendix II, for individual dosing and monitoring for response and toxicity).
  - Ongoing severe pain despite all appropriate treatment above is an indication for urgent referral.

When clinically stable without signs of heart failure, hypotension, bradydysrhythmias or asthma:

- Cardio-selective β-blocker, e.g.:
- Atenolol, oral, 50 mg daily.

- HMGCoA reductase inhibitors (statins), e.g.:

LoE:Ia[xxx]

- Rosuvastatin, oral, 10 mg at night.

Patients on protease inhibitor:

LoE:Ia[xxxi]

- Atorvastatin, oral, 10 mg at night.

Patients on amlodipine (and not on a protease inhibitor):

- Simvastatin, oral, 10–20 mg at night.

If patient complains of muscle pain:
Reduce dose:

- HMGCoA reductase inhibitors (statins), e.g.:

LoE:IIIb[xxxii]

- Simvastatin, oral, 10 mg at night.

OR

LoE:IIIb[xxxiii]

Consult specialist for further management.

If there is cardiac failure or LV dysfunction (see Section 3.4: Congestive cardiac failure):
(I50.0)

- ACE-inhibitor, e.g.:

LoE:IVb[xxxiv]

- Enalapril, oral, target dose 10 mg 12 hourly.

If ACE-inhibitor intolerant, i.e. intractable cough or angio-oedema:

- Angiotensin receptor blocker (ARB), e.g.:
- Losartan, oral, 50–100 mg daily. Specialist initiated.

Institute other therapy for heart failure and LV dysfunction as described in Section 3.4: Congestive cardiac failure.

REFERRAL

» Patients with a diagnosis of acute coronary syndrome should be risk stratified at presentation to estimate their likelihood of developing a major adverse cardiac event (acute MI, heart failure, death or readmission for UA) over the subsequent 4-6 weeks. High risk patients (including those with positive troponins) should be discussed with a cardiology service for consideration for angiography and revascularization therapy. Two widely used and well validated risk stratification scores are TIMI (http://www.mdcalc.com/timi-risk-score-for-uanstemi/) and Grace Risk Scores (http://www.mdcalc.com/grace-acs-risk-and-mortality-calculator). The patient's co-morbidities and willingness to undergo revascularization, which may involve coronary surgery, should be taken into account when advising such referral.

» Other important indications for referral include:
- ongoing chest pain (non-responsive to nitrates, provided PCI facility is available – confirm with cardiologist at referral centre),
- post-infarct angina,
- sustained dysrhythmias,

LoE:IVb[xxxv]

- refractory heart failure,
- refractory cardiogenic shock.

3.2.3 CHRONIC MANAGEMENT OF STEMI / NSTEMI / UA

I25.2/I20.0

GENERAL MEASURES

Lifestyle modification. See Section 3.1: Ischaemic heart disease and atherosclerosis, prevention.

MEDICINE TREATMENT

Continue oral therapy (see Sections 3.2.1: ST elevation myocardial infarction (STEMI) and 3.2.2: Non-ST elevation myocardial infarction (NSTEMI) and unstable angina (UA)).

If heart failure develops, replace atenolol with carvedilol. See Section 3.4: Congestive cardiac failure.

3.2.4 ANGINA PECTORIS, STABLE

I20.I/I20.8-9

DESCRIPTION

Characteristic chest pain due to myocardial ischaemia usually occurring on exercise and relieved by rest. Discomfort may occasionally be experienced

in a site of referral (shoulder, jaw) but the characteristic provocation by exercise and relief by rest is a valuable clue.

GENERAL MEASURES

Lifestyle modification. See Section 3.1: Ischaemic heart disease and atherosclerosis, prevention.

MEDICINE TREATMENT

Long-term prophylaxis for thrombosis:

- Aspirin, oral, 150 mg immediately as a single dose (chewed or dissolved).
  - Followed with 150 mg daily (continued indefinitely in absence of contraindications).

LoE:Ia[xxxvi]

AND

Relief of angina:

- Nitrates, short acting e.g.:
- Isosorbide dinitrate, SL, 5 mg.
  - May be repeated if required at 5-minute intervals for 3 or 4 doses.
  - Instruct patients to keep the tablets in the airtight and lightproof container in which they are supplied.
  - Instruct patients that nitrates are not addictive.
  - Instruct patients to use prophylactically, before activities which may provoke angina.

AND

Step 1

- Cardio-selective β-blocker, e.g.:
- Atenolol, oral, 50–100 mg daily.
  - Titrate to resting heart rate of approximately 60 bpm.

If beta-blocker cannot be tolerated or is contraindicated, use a long-acting calcium channel blocker.

Step 2

ADD

- Long-acting calcium channel blocker, e.g.:
- Amlodipine, oral, 5mg daily.
  - Increase to 10 mg daily if required.

Step 3

ADD

- Organic nitrates, e.g.:
- Isosorbide mononitrate, oral 10–20 mg twice daily.

OR

- Isosorbide dinitrate, oral 20–30 mg twice daily. LoE:IIIb[xxxvii]
  - Take either medicine at 8:00 and 14:00 in order to provide a nitrate-free period to prevent tolerance.

- Modify for night shift workers.

Long-term secondary prophylaxis for coronary artery disease

- HMGCoA reductase inhibitors (statins), e.g.:

LoE:Ia[xxxviii]

- Rosuvastatin, oral, 10 mg at night.

Patients on protease inhibitor:

LoE:Ia[xxxix]

- Atorvastatin, oral, 10 mg at night.

Patients on amlodipine (and not on a protease inhibitor):

- Simvastatin, oral, 10–20 mg at night.

LoE:IIIb[xl]

If patient complains of muscle pain:
Reduce dose:

- HMGCoA reductase inhibitors (statins), e.g.:
- Simvastatin, oral, 10 mg at night.

OR

LoE:IIIb[xli]

Consult specialist for further management.

REFERRAL

» When diagnosis is in doubt, despite exercise stress testing.
» Failed medical therapy. A common reason for "failed" therapy is that the patient has an alternative diagnosis. Therefore, this conclusion should be reached after reasonable effort for non-invasive diagnosis including exercise stress test.

3.2.5 ATHEROSCLEROTIC PERIPHERAL ARTERIAL DISEASE

I70.2, I70.20, I70.21

DESCRIPTION

History and palpation of pulses confirms diagnosis.

GENERAL MEASURES

Smoking cessation is essential and is the single most important intervention to prevent progression.
Exercise within exercise tolerance and other lifestyle modifications.
See Section 3.1: Ischaemic heart disease and atherosclerosis, prevention.

MEDICINE TREATMENT

Long-term prophylaxis for thrombosis:

- Aspirin, oral, 150 mg daily.

AND

- HMGCoA reductase inhibitors (statins), e.g.:

LoE:Ia[xlii]

- Rosuvastatin, oral, 10 mg at night.

Patients on protease inhibitor:

LoE:Iaxliii

- Atorvastatin, oral, 10 mg at night.

Patients on amlodipine (and not on a protease inhibitor):

LoE:IIIb[xliv]

- Simvastatin, oral, 10–20 mg at night.

If patient complains of muscle pain:
Reduce dose:

- HMGCoA reductase inhibitors (statins), e.g.:
- Simvastatin, oral, 10 mg at night.

OR

LoE:IIIb[xlv]

Consult specialist for further management.

Therapy should be initiated together with appropriate lifestyle modification. See Section 3.1: Ischaemic heart disease and atherosclerosis, prevention.

REFERRAL

Ongoing vascular insufficiency, which may be surgically reversible.

3.3 CARDIAC DYSRHYTHMIAS

Exclude underlying structural cardiac disease in all patients with cardiac dysrhythmias (assess patients with an echocardiogram, where available).

3.3.1 NARROW QRS COMPLEX (SUPRAVENTRICULAR) TACHYDYSRHYTHMIAS

I47.1

DESCRIPTION

Sustained (>30 seconds) or non-sustained narrow QRS (≤0.12 seconds) tachycardias.

REFERRAL

» Poor rate control.
» Frequent or severe symptoms for curative radiofrequency catheter ablation.

» All symptomatic Wolf-Parkinson-White (WPW) syndrome patients (sinus rhythm ECG shows delta waves) for radiofrequency catheter ablation.
» Asymptomatic patients in whom the WPW pattern is detected on ECG do not need referral.

3.3.1.1 ATRIAL FIBRILLATION

I48.0-I48.2/I48.9

Acute onset (<48 hours)

Assess clinically, e.g.: heart failure, mitral stenosis, thyrotoxicosis, hypertension, age and other medical conditions.
Consider anticoagulation with warfarin (see table below on CHA_2DS_2-VASc Score).
Synchronised direct current (DC) cardioversion is occasionally necessary in haemodynamic instability.

Non-acute/chronic (>48 hours)

As above, but not immediate DC cardioversion, unless there is haemodynamic instability.

MEDICINE TREATMENT

The main aims of therapy for patients with atrial fibrillation should be:

1. Reduction of stroke and systemic embolic risk.
2. Rate or rhythm control.
3. Relief of symptoms attributed to the atrial fibrillation.

A simple scoring system allows calculation of risk of stroke in patients with non-valvular atrial fibrillation.

CHA_2DS_2-VASc Score:

Risk Factor	Score
Congestive heart failure/LV dysfunction	1
Hypertension	1
Age ≥ 75 years of age	2
Diabetes mellitus	1
Stroke/TIA/Thromboembolism	2
Vascular disease	1
Age 65–74 years of age	1
Sex (female gender)	1

Table 3.4: CHA_2DS_2-VASc Score

Source: Lip GY, Nieuwlaat R, Pisters R, Lane DA, Crijns HJ. Refining clinical risk stratification for predicting stroke and thromboembolism in atrial fibrillation using a novel risk factor-based approach: the euro heart survey on atrial fibrillation. Chest. 2010 Feb;137(2):263-72. http://www.ncbi.nlm.nih.gov/pubmed/19762550

» When the score is ≥2, use warfarin or equivalent. The higher the score the greater the risk of stroke and therefore the more compelling the use of effective anticoagulation.
» **Note:** This score has been developed on patients with non-valvular atrial fibrillation and may not be applicable to patients with atrial fibrillation and

rheumatic mitral valve disease. Anticoagulation has not been tested in this population, but most authorities favour anticoagulation.

HAS-BLED Score:

The potential risk for bleeding needs to be assessed using the HAS-BLED score when initiating oral anticoagulation therapy.

	Risk factor and definitions	Score
H	Uncontrolled hypertension » SBP >160 mmHg	1
A	**Abnormal renal and/or hepatic function** » Dialysis, transplant, serum creatinine >200 mmol/L, cirrhosis, bilirubin >2xULN, AST/ALT/ALP >3xULN	1 point each
S	**Stroke** » Previous ischaemic or haemorrhagic stroke[a]	1
B	**Bleeding history or predisposition** » Previous major haemorrhagic, anaemia, severe thrombocytopenia	1
L	**Labile INR** » TTR ≤60% in patient receiving warfarin	1
E	**Elderly** » Aged >65 years or extreme frailty	1
D	**Drugs or excessive alcohol** » Concomitant use of antiplatelet or NSAID, excessive alcohol per week	1 point each
Maximum score		**9**

Table 3.5: HASBLED Score

a: Haemorrhagic stroke would also score 1 point under the "B" criterion.

b: Only relevant if patient receiving warfarin or other vitamin K antagonists

c: Alcohol excess/abuse refers to a high intake (e.g. >14 units per week) where the clinician assesses there would be an impact on health or bleeding risk

Source: Hindricks G, Potpara T, Dagres N, Arbelo E, Bax JJ, Blomström-Lundqvist C, et al.; ESC Scientific Document Group. 2020 ESC Guidelines for the diagnosis and management of atrial fibrillation developed in collaboration with the European Association for Cardio-Thoracic Surgery (EACTS): The Task Force for the diagnosis and management of atrial fibrillation of the European Society of Cardiology (ESC) Developed with the special contribution of the European Heart Rhythm Association (EHRA) of the ESC. Eur Heart J. 2021 Feb 1;42(5):373-498. https://pubmed.ncbi.nlm.nih.gov/32860505/

» The formal assessment of bleeding risk identifies modifiable bleeding risk factors that should be managed, and patients should be assessed at every visit.

» The higher the score the greater the risk of bleeding.

LoE:IIIa[xlvi]

» A high bleeding risk score should not lead to withholding oral anticoagulation therapy.

Initial therapy aimed at stroke reduction

Anticoagulate with warfarin:

- Warfarin, oral, 5 mg daily.
  - INR should be done after 48 hours, then every 1 to 2 days until within the therapeutic range of 2 to 3 (refer to initiation dosing tables in Appendix II).
  - Adjust dose to keep INR within therapeutic range (refer to maintenance dosing tables in Appendix II).

- Every effort should be made to keep the time in therapeutic range (TTR) >65%. If TTR ≤65% there is less benefit of warfarin therapy and a greater risk of stroke and haemorrhage.

LoE:IIb[xlvii]

See Appendix II for guidance on calculating TTR for management with warfarin.

For therapy aimed at rate control

- Atenolol, oral, 50–100 mg daily.
  - Contraindicated in asthmatics, heart failure.

OR

If in CCF: (I50.0)

- Carvedilol, oral. See Section 3.4: Congestive cardiac failure.

AND

If control not adequate add:

- Digoxin, oral, 0.125 mg daily, adjust according to rate response and trough plasma level
  - Digoxin trough plasma levels (before the morning dose) should be maintained between 0.6-1 nmol/L.
  - Patients at high risk of digoxin toxicity: the elderly, patients with renal dysfunction, hypokalaemia, and patients with low lean body mass.

LoE:IVb[xlviii]

If beta-blockers are contra-indicated, e.g. asthma or severe peripheral vascular disease:

- Verapamil, oral, 40–120 mg 8 hourly.

LoE:IVb[xlix]

  - Titrate against ventricular rate (verapamil is negatively inotropic, therefore avoid in heart failure due to LV dysfunction).

If not controlled on these agents, refer to specialist for consideration of alternative therapy, e.g.: amiodarone or atrioventricular node ablation and pacemaker insertion.

DC cardioversion may be needed in selected cases, after 4 weeks effective warfarin anticoagulation.

Long-term therapy

Continue warfarin anticoagulation long-term, unless contra-indicated:

- Warfarin, oral, 5 mg daily.
  - Control with INR to therapeutic range:

LoE:IIIb[l]

    - INR between 2–3 and patient stable: monitor every 2 months.
    - INR <1.5 or >3.5: monitor monthly.

CAUTION
Warfarin use requires regular INR monitoring and dose adjustment according to measured INR.

For rate control:
- Atenolol, oral, 50–100 mg daily.
  - Contraindicated in asthmatics, heart failure.

If in CCF: (I50.0)
- Carvedilol, oral. See Section 3.4: Congestive cardiac failure.

AND

If control not adequate add:
- Digoxin, oral, start at 0.125 mg daily and adjust according to rate response and trough plasma level.
  - In patients with impaired renal function (eGFR <60 mL/minute), consider 0.125 mg daily and adjust according to trough level monitoring.
  - In all patients, digoxin trough level monitoring is required at all doses.

LoE:IIIb[ii]

If beta-blockers are contra-indicated, e.g. asthma or severe peripheral vascular disease:
- Verapamil, oral, 40–120 mg 8 hourly.
  - Titrate against ventricular rate (verapamil is negatively inotropic, avoid in heart failure due to left ventricular dysfunction).

LoE:IVb[iii]

If not controlled on these agents, refer to specialist for consideration of alternative therapy.

CAUTION
Note: The risk of thromboembolic complications and stroke in those with paroxysmal AF is similar to that of patients with persistent AF and similar recommendations as to anticoagulation apply.

Only in patients with severe symptoms despite the above measures:
- Amiodarone, oral, 200 mg 8 hourly for 1 week. Specialist initiated.
  - Followed by 200 mg 12 hourly for one week.
  - Thereafter, 200 mg daily.

LoE:Ia[iii]

Precautions:
- If on warfarin, halve the dose of warfarin and monitor INR closely, until INR is stable.
- Monitor heart rate closely when patient is on concomitant digoxin.
- Monitor thyroid function every 6 months as thyroid abnormalities may develop.
- Ophthalmological examination every 6 months.

For management of pregnant women with valvular disease and atrial fibrillation, see Section 6.3: Heart disease in pregnancy.

3.3.1.2 ATRIAL FLUTTER

I48.3-4/I48.9

DESCRIPTION

Atrial rate >250 bpm with no flat baseline.
Can be difficult to recognise if 2:1 atrioventricular (AV) block, as the first of the two p waves preceding each QRS complex might be confused with the T-wave of the preceding beat. Vagal stimulation might slow the ventricular rate (usually approximately 150 bpm) and make the dysrhythmia more obvious. Synchronised direct current (DC) cardioversion may be necessary in haemodynamic instability.

MEDICINE TREATMENT

DC cardioversion

DC cardioversion is the most effective therapy and administer midazolam as adjunct therapy:

- Midazolam IV, 1–2.5 mg, administered over 2-3 minutes.

For rate control therapies as for atrial fibrillation: see Section 3.3.1.1 Atrial fibrillation.

CAUTION
Do not use verapamil as it will not convert flutter to sinus rhythm and may cause serious hypotension.

For anticoagulation as per the CHA2DS2-VASc score above: see Section 3.3.1.1 Atrial fibrillation.

If flutter has been present longer than 48 hours, defer cardioversion until after 4 weeks' anticoagulation with warfarin, unless severe symptoms or heart failure require urgent cardioversion.

Long-term therapy

Anticoagulants (See Section 3.3.1.1 Atrial fibrillation). Most consider that the thromboembolic risks in atrial flutter and atrial fibrillation are similar.
Rate control agents as for atrial fibrillation (See Section 3.3.1.1 Atrial fibrillation).
Recurrent atrial flutter is an indication for referral as many may be relatively simply cured by radio-frequency catheter ablation.

3.3.1.3 AV JUNCTIONAL RE-ENTRY TACHYCARDIAS
I47.0

Usually paroxysmal.
Often young patients with normal hearts.
AV nodal re-entry or atrioventricular re-entry (WPW syndrome).
P waves usually not visible (hidden by QRS complexes).

GENERAL MEASURES
Vagal manoeuvres: The modified Valsalva manoeuvre is the most effective – it should be done semi-recumbent with 15 seconds of strain, followed immediately by supine positioning and passive leg raising.
Carotid sinus massage: Should be done with the patient supine and as relaxed as possible.

MEDICINE TREATMENT
Initial therapy
If vagal manoeuvres fail:
- Adenosine, rapid IV bolus, 6 mg.
  - Followed by a bolus of 10 mL sodium chloride 0.9% to ensure that it reaches the heart before it is broken down.
  - Half-life: ± 10 seconds.
  - Run the ECG for 1 minute after the injection as a recording of method of cessation may be helpful diagnostically.
  - If 6 mg fails, repeat with 12 mg.
  - If this fails, repeat with another 12 mg.

» If the medicine reaches the central circulation before it is broken down the patient will experience flushing, sometimes chest pain, wheezing and anxiety.
» If the tachycardia fails to terminate without the patient experiencing those symptoms, the medicine did not reach the heart.

If none of the above is effective or if the patient is hypotensive, consider synchronised cardioversion.

LoE:IVb

Note: Adenosine is contraindicated when atrial flutter is the obvious diagnosis, administration of adenosine can precipitate 1:1 conduction at ventricular rates 250–360 bpm and should be avoided.

Long term therapy
Teach the patient to perform vagal manoeuvres. Valsalva is the most effective.
For infrequent, non-incapacitating symptoms:
- Cardio-selective beta–blocker, e.g.:
- Atenolol, oral, 50–100 mg daily.

LoE:IVb[liv]

If asthmatic, without heart failure:

- Verapamil, oral, 40–120 mg 8 hourly.

Verapamil and digoxin are contraindicated in WPW syndrome

REFERRAL

If the patient continues to experience debilitating symptoms refer for radiofrequency ablation.

3.3.2 WIDE QRS (VENTRICULAR) TACHYARRHYTHMIAS

DESCRIPTION

Sustained (>30 seconds) or non-sustained wide QRS (>0.12 seconds) tachycardias.

3.3.2.1 REGULAR WIDE QRS TACHYCARDIAS

I47.2/I47.9

Regular wide QRS tachycardias are **ventricular** until proved otherwise.
Regular wide QRS supraventricular tachycardias are uncommon.
Refer all cases after resuscitation and stabilisation.
Emergency DC cardioversion is mandatory with a full protocol of cardio-pulmonary resuscitation (CPR) if there is haemodynamic compromise.

GENERAL MEASURES

CPR if necessary.

If no cardiac arrest:

DC cardioversion, 200 J, after sedation with:

- Midazolam, IV, 1–2.5 mg, administered over 2-3 minutes.
  - Monitor and repeat dose after 2-3 minutes, as necessary.

    LoE:IVb
  - If 200 J fails, use 360 J.

If cardiac arrest:

Defibrillate (not synchronised).

MEDICINE TREATMENT

LoE:IVb[iv]

CAUTION

Never give verapamil or adenosine IV to patients with wide QRS tachycardia as this may precipitate ventricular fibrillation.

DC cardioversion **is the preferred and safest first line therapy** for regular wide QRS tachycardias. Medicines are needed if ventricular tachycardia (VT) recurs after cardioversion or spontaneous termination.

LoE:IVb

If in doubt as to the nature of a tachycardia, and in all patients with haemodynamic compromise, DC cardioversion under IV sedation is the safest option.
DC cardioversion, 200 J, after sedation with:

- Midazolam, IV, 1–2.5 mg, administered over 2-3 minutes.
  - Monitor and repeat dose after 2-3 minutes, as necessary.

LoE:IVb

  - If 200 J fails, use 360 J.

- Amiodarone, IV, 5 mg/kg infused over 30 minutes.

Follow with:

- Amiodarone, oral, 200 mg 8 hourly for 7 days.
  - Then, 200 mg 12 hourly for 7 days.
  - Maintenance dose: 200 mg daily for the minimum time required to control the arrhythmia
  - Consult specialist before instituting long-term (>1 week) therapy.

LoE:IVb[lvi]

Precautions:

- If on warfarin, halve the dose of warfarin and monitor INR closely, until INR is stable.
- Monitor heart rate closely when patient is on concomitant digoxin. Monitor thyroid function every 6 months as thyroid abnormalities may develop.
- Ophthalmological examination every 6 months.

REFERRAL

- If no response to DC cardioversion, consult a specialist.

3.3.2.2 SUSTAINED (>30 SECONDS) IRREGULAR WIDE QRS TACHYCARDIAS

I47.0-2/I47.9

These tachycardias are usually due to atrial fibrillation with bundle branch block, or pre-excitation (WPW syndrome).

If the QRS complexes have a pattern of typical right or left bundle branch block, with a rate <170 bpm, treat as for atrial fibrillation. See Section 3.3.1: Narrow QRS complex (supraventricular) tachycardias.

If the rate is >170 bpm, and/or the complexes are atypical or variable, the likely diagnosis is WPW syndrome with atrial fibrillation, conducting via the bypass tract. Treat with DC cardioversion.

Do not treat with medication.
Verapamil and digoxin may precipitate ventricular fibrillation by increasing the ventricular rate.

If in doubt as to the nature of a tachycardia, and in all patients with haemodynamic compromise, DC cardioversion under IV sedation is the safest option.
DC cardioversion, 200 J, after sedation with:

- Midazolam, IV, 1–2.5 mg, administered over 2-3 minutes.
  - Monitor and repeat dose after 2-3 minutes, as necessary.

    LoE:IVb
  - If 200 J fails, use 360 J.

3.3.2.3 NON-SUSTAINED (<30 SECONDS) IRREGULAR WIDE QRS TACHYCARDIAS

I47.0-2/I47.9

These tachycardias are usually ventricular. They are common in acute myocardial infarction. Check serum potassium level and correct if low.

MEDICINE TREATMENT

LoE:IIIb[lvii]

- Amiodarone, IV, 5 mg/kg infused over 30 minutes.

Follow with:

- Amiodarone, oral, 200 mg three times a day for 7 days.
  - Then 200 mg 12 hourly for 7 days.
  - Follow with a maintenance dose of 200–400 mg daily, depending upon clinical judgement. Consult specialist before instituting long-term (>1 week) therapy.

  Precautions:
  - If on warfarin, halve the dose of warfarin and monitor INR closely, until INR is stable.
  - Monitor heart rate closely when patient is on concomitant digoxin.
  - Monitor thyroid function every 6months as thyroid abnormalities may develop.
  - Ophthalmological examination every 6 months.

OR

Only in haemodynamically stable patients:

- Lidocaine (lignocaine), IV, 50–100 mg (1–2 mg/kg) initially as a slow IV injection over 2 minutes.
  - Repeat at 5-minute intervals if required to a total of 200–300 mg.

LoE:IIIb[lviii]

Thereafter, for recurrent ventricular tachycardia only:

- Lidocaine (lignocaine), IV infusion, 1–3 mg/minute for 24–30 hours.

» Lidocaine will only terminate ± 30% of sustained ventricular tachycardias, and may cause hypotension, heart block or convulsions.
» For emergency treatment of ventricular tachycardia, DC cardioversion is first line therapy, even if stable.

In the absence of acute ischaemia or infarction, consider torsades de pointes, due to QT prolonging medicines.

3.3.2.4 Torsades de pointes Ventricular **TACHYCARDIA (VT)**

I47.2

Torsades de pointes Ventricular Tachycardia (VT) has a twisting pattern to the QRS complexes and a prolonged QT interval in sinus rhythm. It is usually due to a QT-prolonging medication, active myocardial ischaemia and/or hypokalaemia and/or a history of alcohol abuse/malnutrition.

GENERAL MEASURES

Defibrillation, as necessary.
Torsades complicating bradycardia: temporary pacing.

MEDICINE TREATMENT

Stop all QT-prolonging medicines (a list of medicines that cause QT prolongation can be viewed at https://www.sads.org.uk/drugs-to-avoid/?doing_wp_cron=1672916576.0519239902496337890625
Correct serum potassium.

- Magnesium sulphate, IV, 2 g administered over 5–10 minutes.

If recurrent episodes after initial dose of magnesium sulphate:

LoE:IVb

- Magnesium sulphate, IV, 2 g administered over 24 hours.

Torsades complicating bradycardia:

- Adrenaline (epinephrine) infusion to raise heart rate to >100 bpm (if temporary pacing unavailable).

REFERRAL

All cases of wide QRS tachycardia, after resuscitation and stabilisation.

3.3.3 HEART BLOCK (SECOND OR THIRD DEGREE)

I44.1/I44.2

DESCRIPTION

The majority of cases occur in patients >60 years of age and are idiopathic, with an excellent long-term prognosis, provided a permanent pacemaker is implanted. Acute, reversible AV block commonly complicates inferior myocardial infarction. Heart block may also be induced by metabolic and electrolyte disturbances, as well as by certain medicines.

GENERAL MEASURES

Emergency cardio-pulmonary resuscitation (if necessary).
External pacemaker should be available in all secondary hospitals and must be preceded by appropriate analgesia.

MEDICINE TREATMENT

Analgesia if external pacemaker:

- Morphine, IM, 10–15 mg 3–6 hourly.

Apply relevant precautions as indicated in Appendix II (i.e. monitoring for response and toxicity).

AV nodal block **with narrow QRS complex escape rhythm only:**

- Atropine, IV bolus, 0.6–1.2 mg.
  - May be repeated as needed until a pacemaker is inserted.
  - Use in patients with inferior myocardial infarct and hypotension and second- degree AV block, if symptomatic.
  - It is temporary treatment of complete AV block before referral (urgently) for pacemaker.

OR

For resuscitation of asystole in combination with CPR:

I46.0-1/I46.9+(I44.1-2)

- Adrenaline (epinephrine) 1:10 000, slow IV, 5 mL (0.5 mg).
  - Used as temporary treatment of complete heart block when other medicines are not effective.

REFERRAL

» All cases with a heart rate <40 bpm after resuscitation and stabilisation.
» All cases of 2nd or 3rd degree AV block, whether or not myocardial infarct or other reversible cause is suspected, and whether or not the patient is thought to be symptomatic.
» A permanent pacemaker is the definitive form of treatment. These are only available in tertiary institutions. Refer all symptomatic patients with significant bradyarrhythmias for evaluation.

3.3.4 SINUS BRADYCARDIA

R00.1

DESCRIPTION

This rhythm does not require treatment, unless it is causing symptoms, i.e. syncope, dizziness, tiredness and poor effort tolerance.

Sinus bradycardia <50 bpm or sinus arrest with slow escape rhythm, accompanied by hypotension, strongly suggest a treatable underlying cause such as:

» acute inferior myocardial infarct,
» hyperkalaemia, especially if wide QRS and/or peaked T waves,
» medicines, especially combination of verapamil and ß-blocker or digoxin,
» hypothermia,
» hypoxia, or
» hypothyroidism.

Treat the cause. Consider atropine if inferior myocardial infarct.

3.3.5 SINUS ARREST

I49.5

Refer all urgently to a cardiologist.

3.4 CONGESTIVE CARDIAC FAILURE (CCF)

I50.0

DESCRIPTION

CCF is a clinical syndrome and has several causes. The cause and immediate precipitating factor(s) of the CCF must be identified and treated to prevent further harm.

Potentially reversible causes include:

» hypertension
» thyroid disease
» valvular heart disease
» constrictive pericarditis
» thiamine deficiency
» ischaemic heart disease
» haemochromatosis
» tachycardia

GENERAL MEASURES

Patient and family education.
Monitor body weight to assess changes in fluid balance.
Limit fluid intake to 1–1.5 L/day if fluid overloaded despite diuretic therapy.
Limit alcohol intake to a maximum 2 drinks per day if at all.

LoE:IIIb[lix]

Salt restriction (dietician guided when possible).
Regular exercise within limits of symptoms.
Avoid NSAIDs as these may exacerbate fluid retention.
Counsel that pregnancy may exacerbate heart failure, and some medicines used in treatment of heart failure are contraindicated in pregnancy e.g. ACE-

inhibitors, angiotensin-receptor blockers, spironolactone.

LoE:IVb[lx]

Advise on contraception or refer for such advice.

MEDICINE TREATMENT

Where heart failure is due to left ventricular systolic dysfunction, mortality is significantly reduced by the use of ACE-inhibitors, beta-blockers and spironolactone and every effort should be made to ensure eligible patients receive all these agents in appropriate doses.

Note: All the guideline evidence presented here relates to treatment of patients in whom the heart failure syndrome is due to left ventricular systolic dysfunction and cannot necessarily be extrapolated to patients in whom heart failure is due to other causes of the syndrome.

Digoxin has only been shown to improve symptoms and reduce hospitalisation.

LoE:Ia[lxi]

Diuretic

Mild volume overload (mild CCF) and normal renal function, thiazide/thiazide-like diuretic e.g.:

LoE:IIIb[lxii]

- Hydrochlorothiazide, oral, 25–50 mg daily.
  - Caution in patients with gout.
  - Less effective in impaired renal function.

LoE:IIIb[lxiii]

  - Caution in patients with a history or family history of skin cancer; and counsel all patients on sun avoidance and sun protection.

Significant volume overload or abnormal renal or hepatic function, loop diuretic:

- Furosemide, oral, daily.
  - Initial dose: 40 mg/day.
  - Higher dosages may be needed, especially if comorbid renal failure.
  - Advise patients to weigh themselves daily and adjust the dose if necessary.

LoE:IVb

Note:

» Unless patient is clinically fluid overloaded, reduce the dose of diuretics before adding an ACE-inhibitor. After introduction of an ACE-inhibitor, try to reduce diuretic dose and consider a change to hydrochlorothiazide.

» Routine use of potassium supplements with diuretics is not recommended. They should be used short-term only, to correct documented low serum potassium level.

LoE:Ia[lxiv]

Renin-angiotensin-aldosterone system (RAAS) blockers

- ACE-inhibitor, e.g.:
- Enalapril, oral, 2.5 mg 12 hourly, titrated to 10 mg 12 hourly.
  - In the absence of significant side-effects always try to increase the dose to the level shown to improve prognosis (i.e. 10 mg 12 hourly).

LoE:Ia[lxv]

If ACE-inhibitor intolerant, i.e. intractable cough or angio-oedema:

- Angiotensin receptor blocker (ARB), e.g.:
- Losartan, oral, 50–100 mg daily. Specialist initiated

Spironolactone

Use with an ACE-inhibitor and furosemide in patients presenting with Class III or IV heart failure.
Do not use if eGFR <30 mL/minute.
Monitoring of potassium levels is essential if spironolactone is used with an ACE-inhibitor or other potassium sparing agent or in the elderly.

- Spironolactone, oral, 25–50 mg once daily.

LoE:IVb[lxvi]

Beta-blockers

For all stable patients with heart failure who tolerate it:
Note: Patients should not be fluid overloaded or have a low BP before initiation of therapy.

- Carvedilol, oral.
  - Initial dose: 3.125 mg 12 hourly.
  - Increase at 2-weekly intervals by doubling the daily dose until a maximum of 25 mg 12 hourly, if tolerated.

LoE:Ia[lxvii]

  - If not tolerated, i.e. worsening of cardiac failure symptoms, reduce the dose to the previously tolerated dose.
  - Up-titration should take several weeks or months.
  - If > 85 kg: maximum of 50 mg 12 hourly.

LoE:IIIb[lxviii]

Digoxin

Patients in sinus rhythm remaining symptomatic despite the above-mentioned agents (specialist consultation):

- Digoxin, oral, 0.125 mg daily, adjust according to response and trough plasma level.
  - Digoxin trough plasma levels (before the morning dose) should be maintained between 0.6-1 nmol/L.
  - Patients at high risk of digoxin toxicity: the elderly, patients with renal dysfunction, hypokalaemia and patients with low lean body mass.

LoE:IIIb[lxix]

Anticoagulants
Heparin: for DVT prophylaxis for patients admitted to hospital, unless contraindicated: See Section 2.14: Venous thrombo-embolism.

Warfarin: See Section 3.3.1: Narrow QRS complex (supraventricular) tachydysrhythmias.

Anti-dysrhythmic medicines
Only for potentially life-threatening ventricular dysrhythmias. See Section 3.3: Cardiac Dysrhythmias.
Always exclude electrolyte abnormalities and medicine toxicity first.

Thiamine
Consider as a trial of therapy in all unexplained heart failure:
- Thiamine, oral/IM, 100 mg daily for 4 weeks.

Prophylaxis (Z29.2)
- Annual influenza vaccine. See Section 9.2: Adult vaccination.

REFERRAL
» Where specialised treatment and diagnostic work-up is needed and to identify treatable and reversible causes.
» All patients with audible cardiac murmurs should undergo specialist evaluation, as should all patients with potentially reversible causes of the heart failure syndrome and those with persistent and severe symptoms and signs of fluid overload despite adequate doses of diuretic.
» Patients who have LBBB on the ECG are potential candidates for cardiac resynchronization therapy and should be discussed with a specialist. An ECG should be recorded at baseline and repeated at 6-monthly intervals.

3.5 ENDOCARDITIS, INFECTIVE
I33.0

GENERAL MEASURES
Bed rest.
Early surgical intervention in acute fulminant and prosthetic valve endocarditis is often indicated. Consider surgery if there is heart failure, embolism, large vegetations on echocardiography, heart block, evidence of persistent infection despite antibiotics or renal impairment. Refer these patients promptly.

LoE:IVb

MEDICINE TREATMENT
Treat accompanying complications, e.g. cardiac failure. Such treatment should not delay referral.

Antibiotic therapy

» It is essential to do at least 3 blood cultures, taken by separate venipunctures, before starting antibiotics.
» In patients with subacute presentation and no haemodynamic compromise, wait for the results of blood culture before starting antibiotics.
» Empiric treatment (Table 4.6) is indicated in patients with a rapidly fulminant course or with severe disease only.
» Aminoglycoside therapy should be monitored with trough levels for safety.
» Duration of therapy listed is the minimum and may be extended based on the response (clinical and laboratory).
» Severe penicillin-allergic patients (Z88.0), or methicillin resistant staphylococcal infections (U80):

LoE:IVb[lxx]

- Vancomycin, IV, 15–20 mg/kg 12 hourly, is the antibiotic of choice. W It is essential to monitor trough concentrations of vancomycin regularly and adjust doses, accordingly, starting after the third dose. (See Appendix II for guidance on prescribing and therapeutic drug monitoring.)

Empiric therapy

Native valve	• Ampicillin, IV, 2 g 6 hourly for 4 weeks. A **AND** LoE:IIIb[lxxi] Gentamicin, IV, 1.5 mg/kg 12 hourly for 2 weeks. (See Appendix II, for guidance on prescribing). A **AND** • Cloxacillin, IV, 3 g, 6 hourly. A **OR** Cefazolin, IV, 2 g, 8 hourly. A
Prosthetic valve*	• Vancomycin, IV, 15–20 mg/kg 12 hourly for 6 weeks. (See Appendix II for guidance on prescribing and therapeutic drug monitoring.) W **AND** • Rifampicin, oral, 7.5 mg/kg 12 hourly for 6 weeks. W **AND** LoE:IIIb[lxxii] • Gentamicin, IV, 1.5 mg/kg 12 hourly for 2 weeks. (See Appendix II for guidance on prescribing). A

* All cases of prosthetic valve endocarditis should be referred.

LoE:IIIb[lxxiii]

Table 3.6: Empiric therapy for valve endocarditis

Directed therapy (native valve)

Streptococcal	
Fully susceptible to penicillin MIC: ≤0.12 mg/L	• Ampicillin, IV, 2 g 6 hourly for 4 weeks. A **OR** Benzylpenicillin (penicillin G), IV, 5 MU 6 hourly for 4 weeks. A
Moderately susceptible MIC: >0.12–2 mg/L	• Ampicillin, IV, 2 g 6 hourly for 4 weeks. A **OR** Benzylpenicillin (penicillin G), IV, 5 MU 6 hourly for 4 weeks. A **AND** LoE:IIIb[lxxiv] • Gentamicin, IV, 3 mg/kg daily for 2 weeks (see Appendix II for guidance on prescribing). A
Fully resistant MIC: ≥4 mg/L	• Vancomycin, IV, 15–20 mg/kg 12 hourly for 6 weeks. W **AND** • Gentamicin, IV, 3 mg/kg daily for 6 weeks (see Appendix II for guidance on prescribing). A LoE:IIIb[lxxv]

Enterococcal	
Susceptible to penicillin	• Ampicillin, IV, 2 g 6 hourly for 4-6 weeks. A **OR** Benzylpenicillin (penicillin G), IV, 5 MU 6 hourly for 4-6 weeks. A ○ 6 weeks of therapy may be required in cases with a history of >3 months, or when the regimen is combined with ceftriaxone. **AND** • Gentamicin, IV, 3 mg/kg daily for 2-6 weeks. A ○ 6 weeks of therapy may be required in cases with a history of >3 months (see Appendix II for guidance on prescribing). Check high level gentamicin susceptibility before prescribing. LoE:IIIb[lxxvi] **OR** LoE:IIIb[lxxvii] • Ceftriaxone 2 g 12-hourly for 6 weeks. W
Penicillin-resistant MIC ≥ 4 mg/L **or** *significant β-lactam allergy*	Refer.
Staphylococcal	
Cloxacillin-susceptible (methicillin-susceptible)	• Cloxacillin, IV, 3 g, 6 hourly for 4 weeks. A LoE:IIIb[lxxviii] **OR** Cefazolin, IV, 2 g, 8 hourly for 4 weeks. A
Cloxacillin-resistant (methicillin resistant) or methicillin sensitive with significant beta-lactam allergy	• Vancomycin, IV, 15–20 mg/kg 12 hourly for 4 weeks. W
	LoE:IIIb[lxxix]

Table 3.7.: Directed therapy for valve endocarditis

Directed therapy for prosthetic valve endocarditis
Duration of therapy is usually a minimum of at least 6 weeks.
Seek expert opinion on antibiotic choice and the need for referral for repeat cardiac surgery early in the course of treatment.

Endocarditis prophylaxis
Cardiac conditions

Patients with the following cardiac conditions are at high risk of developing infective endocarditis:

» Acquired valvular heart disease with stenosis or regurgitation.
» Patients with prosthetic heart valves.
» Structural congenital heart disease, including surgically corrected or palliated structural conditions, but excluding isolated atrial septal defect, fully repaired ventricular septal defect or fully repaired patent ductus arteriosus.
» Patients who have suffered previous endocarditis.

Procedures requiring prophylaxis

Antibiotic prophylaxis is recommended for all dental procedures that involve manipulation of either the gingival tissue or the peri-apical region of the teeth. Antibiotic prophylaxis is not recommended for patients who undergo a gastro-intestinal or genitourinary procedure.

Prophylaxis (Z29.2)

Maintain good dental health.
This is the most important aspect of prophylaxis.
Refer all patients to a dental clinic/dental therapist for assessment and ongoing dental care.

- Amoxicillin, oral, 2 g one hour before the procedure. A

If patient cannot take oral:

- Ampicillin, IV/IM, 2 g one hour before the procedure. A

Severe penicillin allergy: (Z88.0)

- Clindamycin, oral, 600 mg one hour before the procedure. A

If patient with severe penicillin allergy cannot take oral:

- Clindamycin IV, 600 mg one hour before the procedure. A

LoE:IIIb[lxxx]

Note: The NICE review noted the lack of a consistent association between interventional procedures and development of infective endocarditis, and that the efficacy of antibiotic prophylaxis is unproven. It further commented that because the antibiotic is not without risk, there is a potential for a greater mortality from severe hypersensitivity than from withholding antibiotics.

It is very difficult to extrapolate from these guidelines to a South African situation where good dental hygiene may be lacking and valvular heart disease is common. Practitioners need to weigh the risk of the underlying heart disease (particularly previous successfully treated endocarditis) and the essential need for ongoing antibiotic stewardship.

3.6 HYPERTENSION

I10

KEY POINTS

Hypertension control has significant benefit for patients. Detect and treat co-existent risk factors. Assess cardiovascular risk (see Figure 4.1). Lifestyle modification and patient education is essential for all patients.

Classification of hypertension based on office blood pressure			
Category	***Systolic (mmHg)***		***Diastolic (mmHg)***
Normal BP	<130	and	<85
High - Normal	130 - 139	and/or	85 - 89
Mild	140 - 159	and/or	90 - 99
Moderate	160 - 179	and/or	100 - 109
Severe	≥ 180	and/or	≥ 110

LoE:IIIb[lxxxi]

Table 3.8: Classification of hypertension (office-based blood pressures)

Medicine treatment is needed for SBP ≥140 mmHg and DBP ≥90 mmHg that remains elevated despite lifestyle modification.

LoE:IIb[lxxxii]

See medicine treatment choices below.

Immediate medicine treatment is needed for DBP ≥110 mmHg and/or SBP ≥180 mmHg (defined as severe hypertension - see Sections 3.6.1, 3.6.2 and 3.6.3) or for patients with 3 or more risk factors, hypertension mediated organ damage (HMOD) and/or associated clinical conditions.

Patients should be evaluated for cardiovascular risk factors, HMOD and associated clinical conditions.

Other major risk factors for ischaemic cardio- and cerebrovascular disease (see Section 3.1: Ischaemic heart disease and atherosclerosis, prevention).

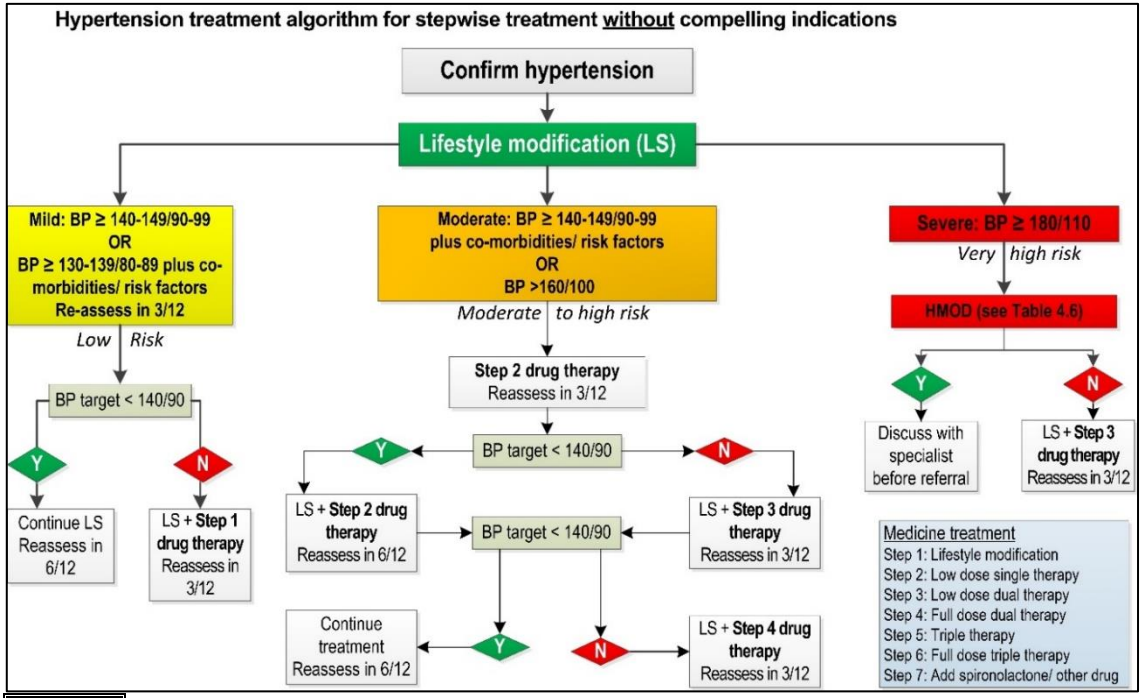
Hypertension mediated organ damage:
» left ventricular hypertrophy,
» hypertensive retinopathy,
» microalbuminuria, or positive dipsticks for albuminuria or elevated albumin/creatinine ratio, or
» elevated creatinine level (or eGFR <60 mL/minute).

Associated clinical conditions:
» ischaemic heart disease,
» heart failure,
» stroke or transient ischaemic attack,
» chronic kidney disease,
» peripheral arterial disease.

Other risk factors, HMOD, or disease	BP (mmHg) grading			
	High normal SBP 130-139 DBP 85-89	Mild SCP 140-159 DBP 90-99	Moderate SBP 160-179 DBP 100-109	Severe SBP≥180 Or DBP ≥110
No other risk factors	Low risk	Low risk	Moderate risk	High risk
1 or 2 risk factors	Low risk	Moderate risk	Moderate to High risk	High risk
≥ 3 risk factors	Low to Moderate risk	Moderate to High risk	High risk	High risk
HMOD, CKD grade 3, or diabetes mellitus without organ damage	Moderate to High risk	High risk	High risk	High to very high risk
Established CVD, CKD grade ≥4, or diabetes mellitus with organ damage	Very high risk	Very high risk	Very high risk	Very high risk

Figure 3.1: Simplified classification of hypertension risk

Source: Williams B, et al. Authors/Task Force Members: 2018 ESC/ESH Guidelines for the management of arterial hypertension: The Task Force for the management of arterial hypertension of the European Society of Cardiology and the European Society of Hypertension. J Hypertens. 2018 Oct;36(10):1953-2041.



LoE:IIIb[lxxxiii]

Caution: Consider monotherapy in low-risk grade 1 hypertension and patients > 80years or the frail (monitor for postural hypotension)

Figure 3.2: Algorithm for the stepwise approach of treating hypertension without compelling indications

Investigations

If overweight, record body weight and waist circumference at each visit when BP is measured. Central obesity is defined as waist circumference:

» >102 cm in men, and
» >88 cm in women.

Do urine test strip analysis for protein, blood and glucose at presentation.

» If normal, repeat urine test strip every 6 months.
» If abnormal, do spot urine ACR. Repeat yearly.
» If haematuria >1+, investigate further.
» If glycosuria, exclude diabetes mellitus.

Other investigations at presentation:

» If known diabetic, HbA1c.
» Random total cholesterol.
» Perform a resting ECG to exclude left ventricular hypertrophy or ischaemia.
» Assess renal function (serum creatinine and eGFR).

Goals of treatment

Aim for SBP <140 mmHg and DBP <90 mmHg.

GENERAL MEASURES

Lifestyle modification

All people with hypertension should be encouraged to make the following lifestyle changes as appropriate.

» Smoking cessation.
» Maintain ideal weight, i.e. BMI 18.5 kg/m^2 to 25 kg/m^2. Weight reduction *LoE:IVb*[lxxxiv] in the overweight patient.
» Salt restriction with increased potassium intake from fresh fruits and vegetables (e.g. remove salt from the table, gradually reduce added salt in food preparation and avoid processed foods). Dietician's advice recommended.
» Reduce alcohol intake to no more than 2 standard drinks per day for males and 1 for females. (1 standard drink = a can of beer = a glass of wine = a shot of spirits.)
» Follow a prudent eating plan i.e. low fat, high fibre and unrefined carbohydrates, with adequate fresh fruit and vegetables. Dietician's advice recommended.
» Regular moderate aerobic exercise, e.g. 30 minutes brisk walking 5-7 times/week (150 minutes/week).

MEDICINE TREATMENT

Initial medicine choice in patients qualifying for treatment is dependent on the presence of compelling indications (see Table 3.9); the severity of the elevated BP; and the presence of target organ damage, cardiovascular risk factors, and associated clinical conditions.

Advise patient to take medication regularly, including on the day of the clinic visit, but a single missed dose does not account for severe elevations in BP.

Note:

» Check adherence to antihypertensive therapy by doing pill counts and questioning family members.

» The use of fixed dose combination medication for control of hypertension may improve adherence and such agents should be used when they are available.

LoE:IIIb[lxxxv]

» Monitor patients monthly and adjust therapy, if necessary, until the BP is controlled.

» After target BP is achieved, patients can be seen at 3–6 monthly intervals.

MEDICINE TREATMENT CHOICES WITHOUT COMPELLING INDICATIONS

Stepped-care approach to BP treatment

Note:

» In low risk (high-normal or mild hypertensive patents) lifestyle intervention may be considered initially, for 3-6 months.

» If lifestyle modification failed to achieve BP control: counsel patient on the risk of major cardiovascular events associated with elevated BP; and initiate monotherapy.

» If BP control is suboptimal: Up titrate treatment (maximise dose of current antihypertensives and/or add additional medicine). Evidence suggests that treatment inertia contributes to suboptimal BP control with patients

LoE:IIIb[lxxxvi]

remaining on monotherapy and/or suboptimal doses.

» The timing of the dose should be guided by the time of day that is most convenient for patients and that would optimize adherence and minimize side effects for individual patients.

» In 60–80% of patients a combination of antihypertensive therapy is needed. Combination therapy, i.e. hydrochlorothiazide plus a calcium channel blocker or ACE-inhibitor should be considered at the outset in patients with BP >160/100 mmHg. Refer to Figures 4.1 and 4.2, above.

» Initiate combination medicine therapy in cases of severe hypertension (see Section 3.6.1) and hypertension urgency (see Section 3.6.2).

BP 140-159/90-99 mmHg:

» < 3 risk factors, no target organ damage or associated clinical conditions:

- Lifestyle modification for 3–6 months.
- Start antihypertensive therapy with a single medicine if target BP not achieved.

» ≥3 risk factors, target organ damage and/or associated clinical conditions:
  – Start antihypertensive therapy immediately (together with lifestyle modification).

BP 160-179/100-109 mmHg:

» Even in absence of risk factors, or target organ damage or associated clinical conditions:
  – Start antihypertensive therapy (together with lifestyle modifications) with a combination of two medicines.

BP ≥180/100 mmHg: this is severe hypertension: see Sections 3.6.1, 3.6.2 and 3.6.3.

Initial antihypertensive medicine:

- thiazide/thiazide-like diuretic e.g.:
- Hydrochlorothiazide, oral, 12.5 mg daily.
  - Caution in patients with gout.
  - Less effective in impaired renal function.
  - Caution in patients with a history or family history of skin cancer; and counsel all patients on sun avoidance and sun protection.

LoE:IIIb[lxxxvii]

If target BP is not reached after one month despite adequate adherence (or immediately in patients with BP 160-179/100-109 mmHg), add one of the following: ACE-inhibitor or calcium channel blocker.

ADD

- Long-acting calcium channel blocker, e.g.:

LoE:IIa[lxxxviii]

- Amlodipine, oral, 5 mg daily.

OR

- ACE-inhibitor, e.g.:

LoE:IIIb[lxxxix]

- Enalapril, oral, 10 mg daily.

If ACE-inhibitor intolerant, i.e. intractable cough:

- Angiotensin receptor blocker (ARB), e.g.:
- Losartan, oral, 50 mg daily. Specialist initiated.

If target BP is still not achieved after one month despite adequate adherence, increase the dose of medication, one medicine every month, to their maximal levels: amlodipine 10 mg daily, enalapril 20 mg daily (losartan 100 mg daily) hydrochlorothiazide 25 mg daily.

If target BP is not reached after one month despite adequate adherence on two medicines, add one of ACE-inhibitor or calcium channel blocker, whichever has not already been used.

If target BP is not reached after one month despite adequate adherence:
ADD

LoE:Ia[xc]

- Spironolactone, oral 25–50 mg daily.

For refractory hypertension:
ADD

LoE:IIb[xci]

- Beta-blocker, e.g.:
- Atenolol, oral, 50 mg daily.

Medicine treatment choices with compelling indications

Compelling indications	Medicine class
Angina	Beta-blocker Calcium channel blocker
Post myocardial infarction	Beta-blocker ACE-inhibitor
Heart failure	ACE-inhibitor Carvedilol Spironolactone Hydrochlorothiazide or furosemide
Left ventricular hypertrophy	ACE-inhibitor
Stroke	Hydrochlorothiazide Calcium channel blocker
Diabetes type 1 or 2 with/without evidence of microalbuminuria or proteinuria	ACE-inhibitor, usually in combination with a diuretic
Chronic kidney disease	ACE-inhibitor, usually in combination with a diuretic
Isolated systolic hypertension	Hydrochlorothiazide Calcium channel blocker
Pregnancy	See Chapter 6: Obstetrics.

Table 3.9: Medicine treatment choices with compelling indications

CAUTION
Lower BP over a few days.
A sudden drop in BP can be dangerous, especially in the elderly.
BP should be controlled within 1–3 months.

Assess for risk of ischaemic disease. See Section 3.1: Ischaemic heart disease and atherosclerosis, prevention.

REFERRAL

Referrals or consultation with a specialist are indicated when:

» Patients are adherent to therapy, and BP is resistant i.e., >140/90 mmHg, while on medicines from 3-4 different classes at appropriate doses, one of which is a diuretic.
» All cases where secondary hypertension is suspected.
» Complicated hypertensive urgency e.g. malignant/accelerated hypertension, severe heart failure with hypertension and hypertensive emergency.

3.6.1 HYPERTENSION, ASYMPTOMATIC SEVERE

I10

DESCRIPTION

These patients have severe hypertension (DBP ≥110 mmHg and/or SBP ≥180 mmHg), are asymptomatic and have no evidence of acute target organ damage.

Keep the patient in the care setting and repeat BP measurement after resting for 1 hour.

If the second measurement is still elevated at the same level, start oral therapy using two medicines together, one of which should be low dose hydrochlorothiazide. The second medicine is either a long-acting calcium channel blocker, e.g., amlodipine, or an ACE-inhibitor, e.g. enalapril.

Follow up carefully and refer as needed.

3.6.2 HYPERTENSIVE URGENCY

I10

DESCRIPTION

Severe hypertension (DBP ≥110 mmHg and/or SBP ≥180 mmHg) which is **symptomatic** and/or with evidence of acutely progressive target organ damage. There are no immediate life threatening neurological or cardiac complications such as are seen in the hypertensive emergencies.

> Do not lower BP in acute stroke or use antihypertensive medication unless SBP >220 mmHg or the DBP >120 mmHg, as a rapid fall in BP may aggravate cerebral ischaemia and worsen the stroke – see Section 14.1.1: Stroke.

Treatment may be given orally but in patients unable to swallow, use parenteral medicines.

MEDICINE TREATMENT

Ideally, all patients with hypertensive urgency should be treated in hospital. Commence treatment with two oral agents and aim to lower the DBP to 100 mmHg slowly over 48–72 hours. Specialist should be consulted.

This BP lowering can be achieved by:

- Long-acting calcium channel blocker.
- ACE-inhibitor.

Note: Avoid if there is severe hyponatraemia, i.e. serum Na <130 mmol/L.

- Spironolactone.
- Beta-blocker.

Diuretics may potentiate the effects of the other classes of medicines when added. Furosemide should be used if there is renal insufficiency or signs of pulmonary congestion.

3.6.3 HYPERTENSIVE CRISIS, HYPERTENSIVE EMERGENCY

I10

DESCRIPTION

This is a **life-threatening situation** that requires immediate lowering of BP usually with parenteral therapy. Grade 3-4 hypertensive retinopathy is usually present, together with impaired renal function and proteinuria.

The true emergency situation should preferably be treated by a specialist.

Life-threatening complications include:

» Hypertensive encephalopathy, i.e. severe headache, visual disturbances, confusion, seizures and coma that may result in cerebral haemorrhage.
» Unstable angina or myocardial infarction.
» Acute left ventricular failure with severe pulmonary oedema (extreme breathlessness at rest).
» Eclampsia and severe pre-eclampsia.
» Acute kidney failure with encephalopathy.
» Acute aortic dissection.

MEDICINE TREATMENT

Admit the patient to a high care setting for intravenous therapy and close monitoring. Do not lower the BP by >25% within 30 minutes to 2 hours.
In the next 2–6 hours, aim to decrease the BP to 160/100 mmHg.
This may be achieved by the use of intravenous or oral medicines.

Intravenous therapy

- Labetalol, IV, 2 mg/minute to a total dose of 1–2 mg/kg, while trying to achieve control with other agents.
  - Caution in acute pulmonary oedema.

OR

If myocardial ischaemia and CCF:

- Glyceryl trinitrate, IV, 5–10 mcg/minute.
  - Refer to dosing table in Section 3.2.1: ST elevation myocardial infarction (STEMI).

AND

- Furosemide, IV, 40–80 mg.
  - Duration of action: 6 hours.
  - Potentiates all of the above medicines.

Oral therapy

- ACE-inhibitor, e.g.:
- Enalapril, oral, 2.5 mg as a test dose.
  - Increase according to response, to a maximum of 20 mg daily.
  - Monitor renal function.

If ACE-inhibitor intolerant, i.e. intractable cough or angio-oedema:

- Angiotensin receptor blocker (ARB), e.g.:
- Losartan, oral, 50–100 mg daily. Specialist initiated.

3.7 RHEUMATIC HEART DISEASE

I01.0-2/I01.8-9, I02.0, I05, I05.1, I06.0-2, I06.8-9, i09.0-2/I09.8-9

DESCRIPTION

These are chronic sequelae of rheumatic fever consisting of valvular damage, usually involving left heart valves, with progression and complications.

GENERAL MEASURES

Acute stage of rheumatic fever: bed rest and supportive care.

MEDICINE TREATMENT

Acute rheumatic fever

For eradication of streptococci in throat:

- Benzathine benzylpenicillin (depot formulation), IM, 1.2 MU as a single dose. A

  LoE:IIIb[xcii]

  - For benzathine benzylpenicillin, IM injection, dissolve benzathine benzylpenicillin 1.2 MU in 3.2 mL lidocaine 1% without adrenaline (epinephrine) or 3 mL water for injection.

OR

LoE:IIb[xciii]

- Amoxicillin, oral, 1 000 mg (1 gram) 12 hourly for 10 days. A

Severe penicillin allergy: (Z88.0) LoE:IIIa[xciv]

- Macrolide, e.g.:
- Azithromycin, oral, 500 mg daily for 3 days. W

For arthritis and fever:

- NSAID, e.g.:

LoE:IVb

- Ibuprofen, oral, 400 mg 8 hourly with meals.

Prevention of recurrent rheumatic fever

All patients with confirmed rheumatic fever and no persistent rheumatic valvular disease:

» Treat for 10 years or until the age of 21 years, whichever is longer.

All patients with confirmed rheumatic fever and persistent rheumatic valvular disease:

LoE:IVb[xcv]

» Treat lifelong.

- Benzathine benzylpenicillin (depot formulation), IM, 1.2 MU every 3–4 weeks (preferred treatment). A
  - For benzathine benzylpenicillin, IM injection, dissolve benzathine benzylpenicillin 1.2 MU in 3.2 mL lidocaine 1% without adrenaline (epinephrine) or 3 mL water for injection.

OR

LoE:IIIb[xcvi]

- Phenoxymethylpenicillin, oral, 250 mg 12 hourly. A

OR

LoE:IVb

- Amoxicillin, oral, 250 mg daily. A

LoE:IVb

Severe penicillin allergy: (Z88.0)

- Macrolide, e.g.:
- Azithromycin, oral, 250 mg daily. W

Prophylaxis for infective endocarditis

See Section 3.5: Endocarditis, infective.

REFERRAL

» Any patient with rheumatic valvular heart disease who requires a significant dose of diuretic to control fluid overload or who has had an episode of pulmonary oedema should be discussed with a specialist and referred for possible valve surgery.

» Pregnancy poses a particular problem in women with symptomatic rheumatic valvular heart disease, and all should be referred for specialist consultation.

References:

[i] Risk factors for prevention of ischaemic heart disease and atherosclerosis (psychological stress):Yusuf S, Hawken S, Ounpuu S, Dans T, Avezum A, Lanas F, McQueen M, Budaj A, Pais P, Varigos J, Lisheng L; INTERHEART Study Investigators. Effect of potentially modifiable risk factors associated with myocardial infarction in 52 countries (the INTERHEART study): case-control study. Lancet. 2004 Sep 11-17;364(9438):937-52. http://www.ncbi.nlm.nih.gov/pubmed/15364185

[ii] Ideal BMI: McGee DL. McGee DL; Diverse Populations Collaboration. Body mass index and mortality: a meta-analysis based on person-level data from twenty-six observational studies. Ann Epidemiol. 2005 Feb;15(2):87-97. https://pubmed.ncbi.nlm.nih.gov/15652713/

Ideal BMI: National Heart, Lung, and Blood Institute in cooperation with The National Institute of Diabetes and Digestive and Kidney Diseases. Clinical Guidelines on the Identification, Evaluation, and Treatment of Overweight and Obesity in Adults, September 1998. Report No.: 98-4083. https://www.ncbi.nlm.nih.gov/books/NBK2003/

[iii] Risk factors for prevention of ischaemic heart disease and atherosclerosis (diabetes): de Vries FM, Kolthof J, Postma MJ, Denig P, Hak E. Efficacy of standard and intensive statin treatment for the secondary prevention of cardiovascular and cerebrovascular events in diabetes patients: a meta-analysis. PLoS One. 2014 Nov 5;9(11):e111247. http://www.ncbi.nlm.nih.gov/pubmed/25372483

[iv] Risk factors for prevention of ischaemic heart disease and atherosclerosis (psychological stress):Yusuf S, Hawken S, Ounpuu S, Dans T, Avezum A, Lanas F, McQueen M, Budaj A, Pais P, Varigos J, Lisheng L; INTERHEART Study Investigators. Effect of potentially modifiable risk factors associated with myocardial infarction in 52 countries (the INTERHEART study): case-control study. Lancet. 2004 Sep 11-17;364(9438):937-52. http://www.ncbi.nlm.nih.gov/pubmed/15364185

[v] Rosuvastatin 10 mg, oral (secondary prevention of ischaemic events): National Department of Health. Affordable Medicines, EDP-Primary Health Care. Cost-effectiveness analysis of high, intermediate, and low dose statins for the secondary prevention of cardiovascular disease, 31 January 2018. https://www.knowledgehub.org.za/content/standard-treatment-guidelines-and-essential-medicines-list

Rosuvastatin 10 mg, oral (secondary prevention of ischaemic events): Cholesterol Treatment Trialists' (CTT) Collaboration. Efficacy and safety of more intensive lowering of LDL cholesterol: a meta-analysis of data from 170 000 participants in 26 randomised trials. The Lancet 2010; 376(9753): 1670-81. https://www.ncbi.nlm.nih.gov/pubmed/21067804

Rosuvastatin 10 mg, oral (secondary prevention of ischaemic events): Naci H, Brugts JJ, Fleurence R, Ades A. Dose-comparative effects of different statins on serum lipid levels: a network meta-analysis of 256,827 individuals in 181 randomized controlled trials. European journal of preventive cardiology 2013; 20(4): 658-70. https://www.ncbi.nlm.nih.gov/pubmed/23529608

[vi] Atorvastatin 10 mg, oral (secondary prevention of ischaemic events – patients on protease inhibitors): Chastain DB, Stover KR, Riche DM. Evidence-based review of statin use in patients with HIV on antiretroviral therapy. J Clin Transl Endocrinol. 2017 Feb 22;8:6-14. https://www.ncbi.nlm.nih.gov/pubmed/29067253

Atorvastatin 10 mg, oral (secondary prevention of ischaemic events – patients on protease inhibitors): National Department of Health. Affordable Medicines, EDP-Primary Health Care. Cost-effectiveness analysis of high, intermediate, and low dose statins for the secondary prevention of cardiovascular disease, 31 January 2018. https://www.knowledgehub.org.za/content/standard-treatment-guidelines-and-essential-medicines-list

Atorvastatin 10 mg, oral (secondary prevention of ischaemic events – patients on protease inhibitors): Cholesterol Treatment Trialists' (CTT) Collaboration. Efficacy and safety of more intensive lowering of LDL cholesterol: a meta-analysis of data from 170 000 participants in 26 randomised trials. The Lancet 2010; 376(9753): 1670-81. https://www.ncbi.nlm.nih.gov/pubmed/21067804

Atorvastatin 10 mg, oral (secondary prevention of ischaemic events – patients on protease inhibitors): Naci H, Brugts JJ, Fleurence R, Ades A. Dose-comparative effects of different statins on serum lipid levels: a network meta-analysis of 256,827 individuals in 181 randomized controlled trials. European journal of preventive cardiology 2013; 20(4): 658-70. https://www.ncbi.nlm.nih.gov/pubmed/23529608

Atorvastatin, oral (drug-drug interaction with protease inhibitors): University of Liverpool. HIV drug interaction database. https://www.hiv-druginteractions.org/

[vii] Simvastatin 40 mg, oral (amlodipine drug interaction): Nishio S, Watanabe H, Kosuge K, Uchida S, Hayashi H, Ohashi K. Interaction between amlodipine and simvastatin in patients with hypercholesterolemia and hypertension. Hypertens Res. 2005;28(3):223–7. https://www.ncbi.nlm.nih.gov/pubmed/16097365

Simvastatin 40 mg, oral (amlodipine drug interaction): Son H, Lee D, Lim LA, Jang SB, Roh H, Park K. Development of a pharmacokinetic interaction model for co-administration of simvastatin and amlodipine. Drug Metab Pharmacokinet. 2014;29(2):120–8. https://www.ncbi.nlm.nih.gov/pubmed/23965645

Simvastatin 40 mg, oral (amlodipine drug interaction): South African Medicines Formulary, 14th Edition. Division of Clinical Pharmacology. University of Cape Town, 2022.

[viii] High dose statins (management of adverse drug reactions): NICE: Cardiovascular disease: risk assessment and reduction, including lipid modification. Clinical guideline, 18 July 2014. www.nice.org.uk/guidance/cg181

[ix] Oxygen: Chu DK, Kim LH, Young PJ, Zamiri N, Almenawer SA, Jaeschke R, Szczeklik W, Schünemann HJ, Neary JD, Alhazzani W. Mortality and morbidity in acutely ill adults treated with liberal versus conservative oxygen therapy (IOTA): a systematic review and meta-analysis. Lancet. 2018 Apr 28;391(10131):1693-1705. https://www.ncbi.nlm.nih.gov/pubmed/29726345

[x] Clopidogrel (STEMI): Chen ZM, Jiang LX, Chen YP, Xie JX, Pan HC, Peto R, Collins R, Liu LS; COMMIT (Clopidogrel and Metoprolol in Myocardial Infarction Trial) collaborative group. Addition of clopidogrel to aspirin in 45,852 patients with acute myocardial infarction: randomised placebo-controlled trial. *Lancet.* 2005 Nov 5;366(9497):1607-21. http://www.ncbi.nlm.nih.gov/pubmed/16271642

[xi] Aspirin, oral (STEMI:100 mg): CURRENT-OASIS 7 Investigators, Mehta SR, Bassand JP, Chrolavicius S, Diaz R, Eikelboom JW, Fox KA, Granger CB, Jolly S, Joyner CD, Rupprecht HJ, Widimsky P, Afzal R, Pogue J, Yusuf S. Dose comparisons of clopidogrel and aspirin in acute coronary syndromes. N Engl J Med. 2010 Sep 2;363(10):930-42. https://www.ncbi.nlm.nih.gov/pubmed/20818903

[xii] Aspirin, oral (stable angina): Antithrombotic Trialists' Collaboration. Collaborative meta-analysis of randomised trials of antiplatelet therapy for prevention of death, myocardial infarction, and stroke in high risk patients.BMJ. 2002 Jan 12;324(7329):71-86. Erratum in: BMJ 2002 Jan 19;324(7330):141. https://www.ncbi.nlm.nih.gov/pubmed/11786451

[xiii] Streptokinase, re-administration: Fears R, et al. Monitoring of streptokinase resistance titre in acute myocardial infarction patients up to 30 months after giving streptokinase or anistreplase and related studies to measure specific antistreptokinase IgG. Br Heart J. 1992 Aug;68(2):167-70. https://pubmed.ncbi.nlm.nih.gov/1389731/

[xiv] Streptokinase: Squire IB, Lawley W, Fletcher S, Holme E, Hillis WS, Hewitt C, Woods KL. Humoral and cellular immune responses up to 7.5 years after administration of streptokinase for acute myocardial infarction.Eur Heart J. 1999 Sep;20(17):1245-52. http://www.ncbi.nlm.nih.gov/pubmed/10454976

Streptokinase: Boersma E, Maas AC, Deckers JW, Simoons ML. Early thrombolytic treatment in acute myocardial infarction: reappraisal of the golden hour. Lancet. 1996 Sep 21;348(9030):771-5. http://www.ncbi.nlm.nih.gov/pubmed/8813982

[xv] Antithrombotic agents: Dundar Y, Hill R, Dickson R, Walley T. Comparative efficacy of thrombolytics in acute myocardial infarction: Asystematic review. QJM - Monthly Journal of the Association of Physicians. 2003;96(2):103-13.https://www.ncbi.nlm.nih.gov/pubmed/12589008

Antithrombotic agents: Thrombolytics (Therapeutic class): National Department of Health: Affordable Medicines, EDP-Adult Hospital level. Medicine Review: Thrombolytics, therapeutic class for STEMI, July 2015. https://www.knowledgehub.org.za/content/standard-treatment-guidelines-and-essential-medicines-list

[xvi] Alteplase, IV (cut-off for tiered dosing): South African Medicines Formulary, 14th Edition. Division of Clinical Pharmacology. University of Cape Town, 2022.

[xvii] Enoxaparin, SC (dosing for treatment of VTE): National Department of Health: Affordable Medicines, EDP-Adult Hospital Level. Medicine Review LMWH vs. UFH for the prophylaxis and treatment of venous thromboembolism and acute coronary syndromes – Appendix A, April 2018. https://www.knowledgehub.org.za/content/standard-treatment-guidelines-and-essential-medicines-list

Low molecular weight heparin (dosing for treatment of VTE): Bhutia S, Wong PF. Once versus twice daily low molecular weight heparin for the initial treatment of venous thromboembolism. Cochrane database Syst Rev. 2013 Jul;(7):CD003074. https://www.ncbi.nlm.nih.gov/pubmed/23857562

Enoxaparin, SC (duration of acute treatment): Efficacy and safety of tenecteplase in combination with enoxaparin, abciximab, or unfractionated heparin: the ASSENT-3 randomised trial in acute myocardial infarction. Lancet (London, England). 2001;358(9282):605-13. https://pubmed.ncbi.nlm.nih.gov/11530146/

Enoxaparin, SC (duration of acute treatment): Ibanez B, James S, Agewall S, Antunes MJ, Bucciarelli-Ducci C, Bueno H, Caforio ALP, et al; ESC Scientific Document Group. 2017 ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation: The Task Force for the management of acute myocardial infarction in patients presenting with ST-segment elevation of the European Society of Cardiology (ESC). Eur Heart J. 2018 Jan 7;39(2):119-177. https://pubmed.ncbi.nlm.nih.gov/28886621/

[xviii] LMWH (adjunctive to alteplase): Eikelboom JW, Quinlan DJ, Mehta SR, Turpie AG, Menown IB, Yusuf S. Unfractionated and low-molecular-weight heparin as adjuncts to thrombolysis in aspirin-treated patients with ST-elevation acute myocardial infarction: a meta-analysis of the randomized trials. Circulation. 2005 Dec 20;112(25):3855-67. https://www.ncbi.nlm.nih.gov/pubmed/16344381

LMWH (adjunctive to alteplase): De Luca G, Marino P. Adjunctive benefits from low-molecular-weight heparins as compared to unfractionated heparin among patients with ST-segment elevation myocardial infarction treated with thrombolysis. A meta-analysis of the randomized trials. Am Heart J. 2007 Dec;154(6):1085.e1-6. https://www.ncbi.nlm.nih.gov/pubmed/18035079

[xix] Nitrates (first line therapy in treatment protocol vs morphine): Meine TJ, Roe MT, Chen AY, Patel MR, Washam JB, Ohman EM, Peacock WF, Pollack CV Jr, Gibler WB, Peterson ED; CRUSADE Investigators. Association of intravenous morphine use and outcomes in acute coronary syndromes: results from the CRUSADE Quality Improvement Initiative. Am Heart J. 2005 Jun;149(6):1043-9. https://www.ncbi.nlm.nih.gov/pubmed/15976786

[xx] Rosuvastatin 10 mg, oral (secondary prevention of ischaemic events): National Department of Health. Affordable Medicines, EDP-Primary Health Care. Cost-effectiveness analysis of high, intermediate, and low dose statins for the

secondary prevention of cardiovascular disease, 31 January 2018. https://www.knowledgehub.org.za/content/standard-treatment-guidelines-and-essential-medicines-list

Rosuvastatin 10 mg, oral (secondary prevention of ischaemic events): Cholesterol Treatment Trialists' (CTT) Collaboration. Efficacy and safety of more intensive lowering of LDL cholesterol: a meta-analysis of data from 170 000 participants in 26 randomised trials. The Lancet 2010; 376(9753): 1670-81. https://www.ncbi.nlm.nih.gov/pubmed/21067804

Rosuvastatin 10 mg, oral (secondary prevention of ischaemic events): Naci H, Brugts JJ, Fleurence R, Ades A. Dose-comparative effects of different statins on serum lipid levels: a network meta-analysis of 256,827 individuals in 181 randomized controlled trials. European journal of preventive cardiology 2013; 20(4): 658-70. https://www.ncbi.nlm.nih.gov/pubmed/23529608

[xxi] Atorvastatin 10 mg, oral (secondary prevention of ischaemic events – patients on protease inhibitors): Chastain DB, Stover KR, Riche DM. Evidence-based review of statin use in patients with HIV on antiretroviral therapy. J Clin Transl Endocrinol. 2017 Feb 22;8:6-14. https://www.ncbi.nlm.nih.gov/pubmed/29067253

Atorvastatin 10 mg, oral (secondary prevention of ischaemic events – patients on protease inhibitors): National Department of Health. Affordable Medicines, EDP-Primary Health Care. Cost-effectiveness analysis of high, intermediate, and low dose statins for the secondary prevention of cardiovascular disease, 31 January 2018. https://www.knowledgehub.org.za/content/standard-treatment-guidelines-and-essential-medicines-list

Atorvastatin 10 mg, oral (secondary prevention of ischaemic events – patients on protease inhibitors): Cholesterol Treatment Trialists' (CTT) Collaboration. Efficacy and safety of more intensive lowering of LDL cholesterol: a meta-analysis of data from 170 000 participants in 26 randomised trials. The Lancet 2010; 376(9753): 1670-81. https://www.ncbi.nlm.nih.gov/pubmed/21067804

Atorvastatin 10 mg, oral (secondary prevention of ischaemic events – patients on protease inhibitors): Naci H, Brugts JJ, Fleurence R, Ades A. Dose-comparative effects of different statins on serum lipid levels: a network meta-analysis of 256,827 individuals in 181 randomized controlled trials. European journal of preventive cardiology 2013; 20(4): 658-70. https://www.ncbi.nlm.nih.gov/pubmed/23529608

Atorvastatin, oral (drug-drug interaction with protease inhibitors): University of Liverpool. HIV drug interaction database. https://www.hiv-druginteractions.org/

[xxii] Simvastatin 40 mg, oral (amlodipine drug interaction): Nishio S, Watanabe H, Kosuge K, Uchida S, Hayashi H, Ohashi K. Interaction between amlodipine and simvastatin in patients with hypercholesterolemia and hypertension. Hypertens Res. 2005;28(3):223–7. https://www.ncbi.nlm.nih.gov/pubmed/16097365

Simvastatin 40 mg, oral (amlodipine drug interaction): Son H, Lee D, Lim LA, Jang SB, Roh H, Park K. Development of a pharmacokinetic interaction model for co-administration of simvastatin and amlodipine. Drug Metab Pharmacokinet. 2014;29(2):120–8. https://www.ncbi.nlm.nih.gov/pubmed/23965645

Simvastatin 40 mg, oral (amlodipine drug interaction): South African Medicines Formulary, 14th Edition. Division of Clinical Pharmacology. University of Cape Town, 2022.

[xxiii] High dose statins (management of adverse drug reactions): NICE: Cardiovascular disease: risk assessment and reduction, including lipid modification. Clinical guideline, 18 July 2014. www.nice.org.uk/guidance/cg181

[xxiv] ACE-inhibitor/angiotensin receptor blocker (caution: drug-drug interaction with fluoroquinolones): Savage R. Ciprofloxacin, enalapril and acute kidney injury: Strengthening of a drug Interaction signal. WHO Pharmaceuticals Newsletter : 16-21, No. 1, 2018. http://www.who.int/medicines/publications/WHO-Pharmaceuticals_Newsletter_No1-2018.pdf?ua=1

ACE-inhibitor/angiotensin receptor blocker (caution: drug-drug interaction with fluoroquinolones): Bird ST, Etminan M, Brophy JM, Hartzema AG, Delaney JA. Risk of acute kidney injury associated with the use of fluoroquinolones. CMAJ. 2013 Jul 9;185(10):E475-82. https://www.ncbi.nlm.nih.gov/pubmed/23734036

[xxv] NSTEMI description: Thygesen K, Alpert JS, Jaffe AS, Chaitman BR, Bax JJ, Morrow DA, White HD; Executive Group on behalf of the Joint European Society of Cardiology (ESC)/American College of Cardiology (ACC)/American Heart Association (AHA)/World Heart Federation (WHF) Task Force for the Universal Definition of Myocardial Infarction. Fourth Universal Definition of Myocardial Infarction (2018). Circulation. 2018 Nov 13;138(20):e618-e651. https://pubmed.ncbi.nlm.nih.gov/30571511/

[xxvi] Oxygen: Chu DK, Kim LH, Young PJ, Zamiri N, Almenawer SA, Jaeschke R, Szczeklik W, Schünemann HJ, Neary JD, Alhazzani W. Mortality and morbidity in acutely ill adults treated with liberal versus conservative oxygen therapy (IOTA): a systematic review and meta-analysis. Lancet. 2018 Apr 28;391(10131):1693-1705. https://www.ncbi.nlm.nih.gov/pubmed/29726345

[xxvii] Clopidogrel (NSTEMI): Yusuf S, Zhao F, Mehta SR, Chrolavicius S, Tognoni G, Fox KK; Clopidogrel in Unstable Angina to Prevent Recurrent Events Trial Investigators. Effects of clopidogrel in addition to aspirin in patients with acute coronary syndromes without ST-segment elevation. N Engl J Med. 2001 Aug 16;345(7):494-502. Erratum in: N Engl J Med 2001 Dec 6;345(23):1716. N Engl J Med 2001 Nov 15;345(20):1506. http://www.ncbi.nlm.nih.gov/pubmed/11519503

Clopidogrel (NSTEMI): Yusuf S, Mehta SR, Zhao F, Gersh BJ, Commerford PJ, Blumenthal M, Budaj A, Wittlinger T, Fox KA; Clopidogrel in Unstable angina to prevent Recurrent Events Trial Investigators. Early and late effects of clopidogrel in patients with acute coronary syndromes.Circulation. 2003 Feb 25;107(7):966-72. http://www.ncbi.nlm.nih.gov/pubmed/12600908

[xxviii] Aspirin, oral (NSTEMI): Peters RJ, Mehta SR, Fox KA, Zhao F, Lewis BS, Kopecky SL, Diaz R, Commerford PJ, Valentin V, Yusuf S; Clopidogrel in Unstable angina to prevent Recurrent Events (CURE) Trial Investigators. Effects of

aspirin dose when used alone or in combination with clopidogrel in patients with acute coronary syndromes: observations from the Clopidogrel in Unstable angina to prevent Recurrent Events (CURE) study. Circulation. 2003 Oct 7;108(14):1682-7. https://www.ncbi.nlm.nih.gov/pubmed/14504182

[xxix] Parenteral anticoagulation (NSTEMI, UA): Andrade-Castellanos CA, Colunga-Lozano LE, Delgado-Figueroa N, Magee K. Heparin versus placebo for non-ST elevation acute coronary syndromes. CochraneDatabaseSyst Rev. 2014 Jun 27;6:CD003462.http://www.ncbi.nlm.nih.gov/pubmed/24972265

Parenteral anticoagulation (NSTEMI, UA):Ferguson JJ, Califf RM, Antman EM, Cohen M, Grines CL, Goodman S, KereiakesDJ, Langer A, Mahaffey KW, Nessel CC, Armstrong PW, Avezum A, Aylward P, Becker RC, Biasucci L, Borzak S, Col J, Frey MJ, Fry E, Gulba DC, Guneri S, Gurfinkel E, Harrington R, Hochman JS, Kleiman NS, Leon MB, Lopez-Sendon JL, PepineCJ, Ruzyllo W, Steinhubl SR, Teirstein PS, Toro-Figueroa L, White H; SYNERGY Trial Investigators. Enoxaparin vs unfractionated heparin in high-risk patients with non-ST-segment elevation acute coronary syndromes managed with an intended early invasive strategy: primary results of the SYNERGY randomized trial. JAMA. 2004 Jul 7;292(1):45-54. http://www.ncbi.nlm.nih.gov/pubmed/15238590

Parenteral anticoagulation (NSTEMI, UA):Cohen M, Demers C, Gurfinkel EP, Turpie AG, Fromell GJ, Goodman S, Langer A, Califf RM, Fox KA, Premmereur J, Bigonzi F. A comparison of low-molecular-weight heparin with unfractionated heparin for unstable coronary artery disease. Efficacy and Safety of Subcutaneous Enoxaparin in Non-Q-Wave Coronary Events Study Group. N Engl J Med. 1997 Aug 14;337(7):447-52.http://www.ncbi.nlm.nih.gov/pubmed/9250846

Parenteral anticoagulation (NSTEMI, UA):Amsterdam EA, Wenger NK, Brindis RG, Casey DE Jr, GaniatsTG, Holmes DR Jr, Jaffe AS, Jneid H, Kelly RF, Kontos MC, Levine GN, Liebson PR, Mukherjee D, Peterson ED, Sabatine MS, Smalling RW, Zieman SJ; American College of Cardiology; American Heart Association Task Force on Practice Guidelines; Society for Cardiovascular Angiography and Interventions; Society of Thoracic Surgeons; American Association for Clinical Chemistry. 2014 AHA/ACC Guideline for the Management of Patients with Non-ST-Elevation Acute Coronary Syndromes: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. J Am CollCardiol. 2014 Dec 23;64(24):e139-228.http://www.ncbi.nlm.nih.gov/pubmed/25260718

[xxx] Rosuvastatin 10 mg, oral (secondary prevention of ischaemic events): National Department of Health. Affordable Medicines, EDP-Primary Health Care. Cost-effectiveness analysis of high, intermediate, and low dose statins for the secondary prevention of cardiovascular disease, 31 January 2018. https://www.knowledgehub.org.za/content/standard-treatment-guidelines-and-essential-medicines-list

Rosuvastatin 10 mg, oral (secondary prevention of ischaemic events): Cholesterol Treatment Trialists' (CTT) Collaboration. Efficacy and safety of more intensive lowering of LDL cholesterol: a meta-analysis of data from 170 000 participants in 26 randomised trials. The Lancet 2010; 376(9753): 1670-81. https://www.ncbi.nlm.nih.gov/pubmed/21067804

Rosuvastatin 10 mg, oral (secondary prevention of ischaemic events): Naci H, Brugts JJ, Fleurence R, Ades A. Dose-comparative effects of different statins on serum lipid levels: a network meta-analysis of 256,827 individuals in 181 randomized controlled trials. European journal of preventive cardiology 2013; 20(4): 658-70. https://www.ncbi.nlm.nih.gov/pubmed/23529608

[xxxi] Atorvastatin 10 mg, oral (secondary prevention of ischaemic events – patients on protease inhibitors): Chastain DB, Stover KR, Riche DM. Evidence-based review of statin use in patients with HIV on antiretroviral therapy. J Clin Transl Endocrinol. 2017 Feb 22;8:6-14. https://www.ncbi.nlm.nih.gov/pubmed/29067253

Atorvastatin 10 mg, oral (secondary prevention of ischaemic events – patients on protease inhibitors): National Department of Health. Affordable Medicines, EDP-Primary Health Care. Cost-effectiveness analysis of high, intermediate, and low dose statins for the secondary prevention of cardiovascular disease, 31 January 2018. https://www.knowledgehub.org.za/content/standard-treatment-guidelines-and-essential-medicines-list

Atorvastatin 10 mg, oral (secondary prevention of ischaemic events – patients on protease inhibitors): Cholesterol Treatment Trialists' (CTT) Collaboration. Efficacy and safety of more intensive lowering of LDL cholesterol: a meta-analysis of data from 170 000 participants in 26 randomised trials. The Lancet 2010; 376(9753): 1670-81. https://www.ncbi.nlm.nih.gov/pubmed/21067804

Atorvastatin 10 mg, oral (secondary prevention of ischaemic events – patients on protease inhibitors): Naci H, Brugts JJ, Fleurence R, Ades A. Dose-comparative effects of different statins on serum lipid levels: a network meta-analysis of 256,827 individuals in 181 randomized controlled trials. European journal of preventive cardiology 2013; 20(4): 658-70. https://www.ncbi.nlm.nih.gov/pubmed/23529608

Atorvastatin, oral (drug-drug interaction with protease inhibitors): University of Liverpool. HIV drug interaction database. https://www.hiv-druginteractions.org/

[xxxii] Simvastatin 40 mg, oral (amlodipine drug interaction): Nishio S, Watanabe H, Kosuge K, Uchida S, Hayashi H, Ohashi K. Interaction between amlodipine and simvastatin in patients with hypercholesterolemia and hypertension. Hypertens Res. 2005;28(3):223–7. https://www.ncbi.nlm.nih.gov/pubmed/16097365

Simvastatin 40 mg, oral (amlodipine drug interaction): Son H, Lee D, Lim LA, Jang SB, Roh H, Park K. Development of a pharmacokinetic interaction model for co-administration of simvastatin and amlodipine. Drug Metab Pharmacokinet. 2014;29(2):120–8. https://www.ncbi.nlm.nih.gov/pubmed/23965645

Simvastatin 40 mg, oral (amlodipine drug interaction): South African Medicines Formulary, 14th Edition. Division of Clinical Pharmacology. University of Cape Town, 2022.

[xxxiii] High dose statins (management of adverse drug reactions): NICE: Cardiovascular disease: risk assessment and reduction, including lipid modification. Clinical guideline, 18 July 2014. www.nice.org.uk/guidance/cg181

[xxxiv] Enalapril: South African Medicines Formulary, 14th Edition. Division of Clinical Pharmacology. University of Cape Town, 2022.

[xxxv] Chronic ACS (referral – cardiogenic shock): Collet J-P, Thiele H, Barbato E, Barthélémy O, Bauersachs J, Bhatt DL, et al. 2020 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation: The Task Force for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation of the European Society of Cardiology (ESC). Eur Heart J. 2020;42(14):1289-367. https://pubmed.ncbi.nlm.nih.gov/32860058/

[xxxvi] Aspirin, oral (stable angina): Antithrombotic Trialists' Collaboration. Collaborative meta-analysis of randomised trials of antiplatelet therapy for prevention of death, myocardial infarction, and stroke in high risk patients.BMJ. 2002 Jan 12;324(7329):71-86. Erratum in: BMJ 2002 Jan 19;324(7330):141. https://www.ncbi.nlm.nih.gov/pubmed/11786451

[xxxvii] Organic nitrates (Isosorbide mononitrate and dinitrate, oral): Thadani U, Lipicky RJ. Short and long-acting oral nitrates for stable angina pectoris.Cardiovasc Drugs Ther. 1994 Aug;8(4):611-23. https://www.ncbi.nlm.nih.gov/pubmed/7848896

Organic nitrates (Isosorbide mononitrate and dinitrate, oral): Parker JO. Eccentric dosing with isosorbide-5-mononitrate in angina pectoris.Am J Cardiol. 1993 Oct 15;72(12):871-6. https://www.ncbi.nlm.nih.gov/pubmed/8213541

[xxxviii] Rosuvastatin 10 mg, oral (secondary prevention of ischaemic events): National Department of Health. Affordable Medicines, EDP-Primary Health Care. Cost-effectiveness analysis of high, intermediate, and low dose statins for the secondary prevention of cardiovascular disease, 31 January 2018. https://www.knowledgehub.org.za/content/standard-treatment-guidelines-and-essential-medicines-list

Rosuvastatin 10 mg, oral (secondary prevention of ischaemic events): Cholesterol Treatment Trialists' (CTT) Collaboration. Efficacy and safety of more intensive lowering of LDL cholesterol: a meta-analysis of data from 170 000 participants in 26 randomised trials. The Lancet 2010; 376(9753): 1670-81. https://www.ncbi.nlm.nih.gov/pubmed/21067804

Rosuvastatin 10 mg, oral (secondary prevention of ischaemic events): Naci H, Brugts JJ, Fleurence R, Ades A. Dose-comparative effects of different statins on serum lipid levels: a network meta-analysis of 256,827 individuals in 181 randomized controlled trials. European journal of preventive cardiology 2013; 20(4): 658-70. https://www.ncbi.nlm.nih.gov/pubmed/23529608

[xxxix] Atorvastatin 10 mg, oral (secondary prevention of ischaemic events – patients on protease inhibitors): Chastain DB, Stover KR, Riche DM. Evidence-based review of statin use in patients with HIV on antiretroviral therapy. J Clin Transl Endocrinol. 2017 Feb 22;8:6-14. https://www.ncbi.nlm.nih.gov/pubmed/29067253

Atorvastatin 10 mg, oral (secondary prevention of ischaemic events – patients on protease inhibitors): National Department of Health. Affordable Medicines, EDP-Primary Health Care. Cost-effectiveness analysis of high, intermediate, and low dose statins for the secondary prevention of cardiovascular disease, 31 January 2018. https://www.knowledgehub.org.za/content/standard-treatment-guidelines-and-essential-medicines-list

Atorvastatin 10 mg, oral (secondary prevention of ischaemic events – patients on protease inhibitors): Cholesterol Treatment Trialists' (CTT) Collaboration. Efficacy and safety of more intensive lowering of LDL cholesterol: a meta-analysis of data from 170 000 participants in 26 randomised trials. The Lancet 2010; 376(9753): 1670-81. https://www.ncbi.nlm.nih.gov/pubmed/21067804

Atorvastatin 10 mg, oral (secondary prevention of ischaemic events – patients on protease inhibitors): Naci H, Brugts JJ, Fleurence R, Ades A. Dose-comparative effects of different statins on serum lipid levels: a network meta-analysis of 256,827 individuals in 181 randomized controlled trials. European journal of preventive cardiology 2013; 20(4): 658-70. https://www.ncbi.nlm.nih.gov/pubmed/23529608

Atorvastatin, oral (drug-drug interaction with protease inhibitors): University of Liverpool. HIV drug interaction database. https://www.hiv-druginteractions.org/

[xl] Simvastatin 40 mg, oral (amlodipine drug interaction): Nishio S, Watanabe H, Kosuge K, Uchida S, Hayashi H, Ohashi K. Interaction between amlodipine and simvastatin in patients with hypercholesterolemia and hypertension. Hypertens Res. 2005;28(3):223–7. https://www.ncbi.nlm.nih.gov/pubmed/16097365

Simvastatin 40 mg, oral (amlodipine drug interaction): Son H, Lee D, Lim LA, Jang SB, Roh H, Park K. Development of a pharmacokinetic interaction model for co-administration of simvastatin and amlodipine. Drug Metab Pharmacokinet. 2014;29(2):120–8. https://www.ncbi.nlm.nih.gov/pubmed/23965645

Simvastatin 40 mg, oral (amlodipine drug interaction): South African Medicines Formulary, 14th Edition. Division of Clinical Pharmacology. University of Cape Town, 2022.

[xli] High dose statins (management of adverse drug reactions): NICE: Cardiovascular disease: risk assessment and reduction, including lipid modification. Clinical guideline, 18 July 2014. www.nice.org.uk/guidance/cg181

[xlii] Rosuvastatin 10 mg, oral (secondary prevention of ischaemic events): National Department of Health. Affordable Medicines, EDP-Primary Health Care. Cost-effectiveness analysis of high, intermediate, and low dose statins for the secondary prevention of cardiovascular disease, 31 January 2018. https://www.knowledgehub.org.za/content/standard-treatment-guidelines-and-essential-medicines-list

Rosuvastatin 10 mg, oral (secondary prevention of ischaemic events): Cholesterol Treatment Trialists' (CTT) Collaboration. Efficacy and safety of more intensive lowering of LDL cholesterol: a meta-analysis of data from 170 000 participants in 26 randomised trials. The Lancet 2010; 376(9753): 1670-81. https://www.ncbi.nlm.nih.gov/pubmed/21067804

Rosuvastatin 10 mg, oral (secondary prevention of ischaemic events): Naci H, Brugts JJ, Fleurence R, Ades A. Dose-comparative effects of different statins on serum lipid levels: a network meta-analysis of 256,827 individuals in

181 randomized controlled trials. European journal of preventive cardiology 2013; 20(4): 658-70. https://www.ncbi.nlm.nih.gov/pubmed/23529608

[xliii] Atorvastatin 10 mg, oral (secondary prevention of ischaemic events – patients on protease inhibitors): Chastain DB, Stover KR, Riche DM. Evidence-based review of statin use in patients with HIV on antiretroviral therapy. J Clin Transl Endocrinol. 2017 Feb 22;8:6-14. https://www.ncbi.nlm.nih.gov/pubmed/29067253

Atorvastatin 10 mg, oral (secondary prevention of ischaemic events – patients on protease inhibitors): National Department of Health. Affordable Medicines, EDP-Primary Health Care. Cost-effectiveness analysis of high, intermediate, and low dose statins for the secondary prevention of cardiovascular disease, 31 January 2018. https://www.knowledgehub.org.za/content/standard-treatment-guidelines-and-essential-medicines-list

Atorvastatin 10 mg, oral (secondary prevention of ischaemic events – patients on protease inhibitors): Cholesterol Treatment Trialists' (CTT) Collaboration. Efficacy and safety of more intensive lowering of LDL cholesterol: a meta-analysis of data from 170 000 participants in 26 randomised trials. The Lancet 2010; 376(9753): 1670-81. https://www.ncbi.nlm.nih.gov/pubmed/21067804

Atorvastatin 10 mg, oral (secondary prevention of ischaemic events – patients on protease inhibitors): Naci H, Brugts JJ, Fleurence R, Ades A. Dose-comparative effects of different statins on serum lipid levels: a network meta-analysis of 256,827 individuals in 181 randomized controlled trials. European journal of preventive cardiology 2013; 20(4): 658-70. https://www.ncbi.nlm.nih.gov/pubmed/23529608

Atorvastatin, oral (drug-drug interaction with protease inhibitors): University of Liverpool. HIV drug interaction database. https://www.hiv-druginteractions.org/

[xliv] Simvastatin 40 mg, oral (amlodipine drug interaction): Nishio S, Watanabe H, Kosuge K, Uchida S, Hayashi H, Ohashi K. Interaction between amlodipine and simvastatin in patients with hypercholesterolemia and hypertension. Hypertens Res. 2005;28(3):223–7. https://www.ncbi.nlm.nih.gov/pubmed/16097365

Simvastatin 40 mg, oral (amlodipine drug interaction): Son H, Lee D, Lim LA, Jang SB, Roh H, Park K. Development of a pharmacokinetic interaction model for co-administration of simvastatin and amlodipine. Drug Metab Pharmacokinet. 2014;29(2):120–8. https://www.ncbi.nlm.nih.gov/pubmed/23965645

Simvastatin 40 mg, oral (amlodipine drug interaction): South African Medicines Formulary, 14th Edition. Division of Clinical Pharmacology. University of Cape Town, 2022.

[xlv] High dose statins (management of adverse drug reactions): NICE: Cardiovascular disease: risk assessment and reduction, including lipid modification. Clinical guideline, 18 July 2014. www.nice.org.uk/guidance/cg181

[xlvi] HAS-BLED Score (Bleeding risk in atrial fibrillation): Chang G, Xie Q, Ma L, Hu K, Zhang Z, Mu G, et al. Accuracy of HAS-BLED and other bleeding risk assessment tools in predicting major bleeding events in atrial fibrillation: A network meta-analysis. J Thromb Haemost. 2020;18(4):791-801. https://pubmed.ncbi.nlm.nih.gov/31782613/

HAS-BLED Score (Bleeding risk in atrial fibrillation): Pisters R, Lane DA, Nieuwlaat R, de Vos CB, Crijns HJ, Lip GY. A novel userfriendly score (HAS-BLED) to assess 1-year risk of major bleeding in patients with atrial fibrillation: the Euro Heart Survey. Chest 2010;138:10931100. https://pubmed.ncbi.nlm.nih.gov/20299623/

[xlvii] Warfarin, oral (time in therapeutic range): Wan Y, Heneghan C, Perera R, RobertsN, Hollowell J, Glasziou P, et al. Anticoagulation control and prediction of adverse events in patients with atrial fibrillation: a systematic review. Circ Cardiovasc Qual Outcomes 2008;1:84_91. https://pubmed.ncbi.nlm.nih.gov/20031794/

[xlviii] Warfarin, oral (time in therapeutic range): Connolly SJ, Pogue J, Eikelboom J, Flaker G, Commerford P, Franzosi MG, Healey JS, Yusuf S; ACTIVE W Investigators. Benefit of oral anticoagulant over antiplatelet therapy in atrial fibrillation depends on the quality of international normalized ratio control achieved by centers and countries as measured by time in therapeutic range. Circulation. 2008 Nov 11;118(20):2029-37. https://pubmed.ncbi.nlm.nih.gov/18955670/

Opie LH, Gersh B. Drugs for the heart; 8th Edition 2009 P 204, Table 6-7

[xlix] Verapamil: South African Medicines Formulary, 14th Edition. Division of Clinical Pharmacology. University of Cape Town, 2022.

[l] Warfarin, oral (2-monthly INR monitoring): Rosendaal FR, Cannegieter SC, van der Meer FJ, Briët E. A method to determine the optimal intensity of oral anticoagulant therapy. Thromb Haemost. 1993 Mar 1;69(3):236-9. https://pubmed.ncbi.nlm.nih.gov/8470047/

Warfarin, oral (2-monthly INR monitoring): zar AJ, Cannegieter SC, Deckers JW, Briët E, van Bergen PF, Jonker JJ, Rosendaal FR. Optimal intensity of oral anticoagulant therapy after myocardial infarction. J Am Coll Cardiol. 1996 May;27(6):1349-55. https://pubmed.ncbi.nlm.nih.gov/8626943/

Warfarin, oral (2-monthly INR monitoring): Rose AJ, Miller DR, Ozonoff A, Berlowitz DR, Ash AS, Zhao S, Reisman JI, Hylek EM. Gaps in monitoring during oral anticoagulation: insights into care transitions, monitoring barriers, and medication nonadherence. Chest. 2013 Mar;143(3):751-757. https://pubmed.ncbi.nlm.nih.gov/23187457/

[li] Digoxin: Fauchier L, Laborie G, Clementy N, Bernard A, Angoulvant D, Lip GHY, Babuty D. Effect of digoxin on all-cause mortality in patients with atrial fibrillation in a population-based cohort study. Heart Failure Congress; May 24, 2015; Seville, Spain.Presentation 539.https://www.escardio.org/

Digoxin: South African Medicines Formulary, 14th Edition. Division of Clinical Pharmacology. University of Cape Town, 2022.

[lii] Verapamil: South African Medicines Formulary, 14th Edition. Division of Clinical Pharmacology. University of Cape Town, 2022.

[liii] Amiodarone, oral (after cardioversion of atrial fibrillation): Valembois L, Audureau E, Takeda A, Jarzebowski W, Belmin J, Lafuente-Lafuente C. Antiarrhythmics for maintaining sinus rhythm after cardioversion of atrial fibrillation. Cochrane Database Syst Rev. 2019 Sep 4;9(9):CD005049. https://pubmed.ncbi.nlm.nih.gov/31483500/

[liv] Verapamil: South African Medicines Formulary, 14th Edition. Division of Clinical Pharmacology. University of Cape Town, 2022.

[lv] Adenosine: South African Medicines Formulary, 14th Edition. Division of Clinical Pharmacology. University of Cape Town, 2022.

[lvi] Amiodarone, oral (dosing): Joint Formulary Committee. British National Formulary. London: BMJ Group and Pharmaceutical Press; 2022.

[lvii] Salt restriction (CCF): McDonagh TA, Metra M, Adamo M, Gardner RS, Baumbach A, Böhm M, et al; ESC Scientific Document Group. 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. Eur Heart J. 2021 Sep 21;42(36):3599-3726. https://pubmed.ncbi.nlm.nih.gov/34447992/

[lviii] Lignocaine slow IV injection: professional Information Leaflet. Lignocaine HCl Fresenius 10 % (Ampoules) solution for injection. Fresenius Kabi Manufacturing SA (Pty) Ltd. Date of revision of text: 2 September 2020.
South African Medicines Formulary, 14th Edition. Division of Clinical Pharmacology. University of Cape Town, 2022.

[lix] Amiodarone, oral dose: Professional Information Leaflet. Amiodarone hydrochloride 200mg tablets. Biotech Laboratories (Pty) Ltd. Date of first authorization/renewal of authorization: 24 January 2003.

[lx] Pregnancy – medicines contraindicated: South African Medicines Formulary, 14th Edition. Division of Clinical Pharmacology. University of Cape Town, 2022.

[lxi] Digoxin: Digitalis Investigation Group. The effect of digoxin on mortality and morbidity in patients with heart failure. N Engl J Med. 1997 Feb 20;336(8):525-33. http://www.ncbi.nlm.nih.gov/pubmed/9036306

[lxii] Hydrochlorothiazide, oral (mild CCF): McDonagh TA, Metra M, Adamo M, Gardner RS, Baumbach A, Böhm M, et al; ESC Scientific Document Group. 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. Eur Heart J. 2021 Sep 21;42(36):3599-3726. https://pubmed.ncbi.nlm.nih.gov/34447992/

[lxiii] Hydrochlorothiazide, oral (skin cancer risk): Pedersen SA, Gaist D, Schmidt SAJ, Hölmich LR, Friis S, Pottegård A. Hydrochlorothiazide use and risk of nonmelanoma skin cancer: A nationwide case-control study from Denmark. J Am Acad Dermatol. 2018 Apr;78(4):673-681.e9. https://www.ncbi.nlm.nih.gov/pubmed/29217346

Hydrochlorothiazide, oral (skin cancer risk): Pottegård A, Hallas J, Olesen M, Svendsen MT, Habel LA, Friedman GD, Friis S. Hydrochlorothiazide use is strongly associated with risk of lip cancer. J Intern Med. 2017 Oct;282(4):322-331. https://www.ncbi.nlm.nih.gov/pubmed/28480532

Hydrochlorothiazide, oral (skin cancer risk): National Department of Health, Essential Drugs Programme: Updated Notice: Risk of skin cancer associated with hydrochlorothiazide, 6 March 2019. http://www.health.gov.za/

[lxiv] ACE-inhibtors (first-line option for CCF): Tai C, Gan T, Zou L, Sun Y, Zhang Y, Chen W, Li J, Zhang J, Xu Y, Lu H, Xu D. Effect of angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers on cardiovascular events in patients with heart failure: a meta-analysis of randomized controlled trials. BMC Cardiovasc Disord. 2017 Oct 5;17(1):257. https://www.ncbi.nlm.nih.gov/pubmed/28982370

[lxv] Enalapril target dose: Effect of enalapril on survival in patients with reduced left ventricular ejection fractions and congestive heart failure. The SOLVD Investigators. N EnglJ Med. 1991 Aug 1;325(5):293-302. http://www.ncbi.nlm.nih.gov/pubmed/2057034

Enalapril target dose: Effect of enalapril on mortality and the development of heart failure in asymptomatic patients with reduced left ventricular ejection fractions. The SOLVD Investigators. N Engl J Med. 1992 Sep 3;327(10):685-91. Erratum in: N Engl J Med 1992 Dec 10;327(24):1768. http://www.ncbi.nlm.nih.gov/pubmed/1463530

Enalapril target dose: CONSENSUS Trial Study Group. Effects of enalapril on mortality in severe congestive heart failure. Results of the Cooperative North Scandinavian Enalapril Survival Study (CONSENSUS). N Engl J Med. 1987 Jun 4;316(23):1429-35. https://www.ncbi.nlm.nih.gov/pubmed/2883575

[lxvi] Spironolactone: South African Medicines Formulary, 14th Edition. Division of Clinical Pharmacology. University of Cape Town, 2022.

[lxvii] Carvedilol: Packer M, Coats AJ, Fowler MB, Katus HA, Krum H, Mohacsi P, Rouleau JL, Tendera M, Castaigne A, Roecker EB, Schultz MK, DeMets DL; Carvedilol Prospective Randomized Cumulative Survival Study Group. Effect of carvedilol on survival in severe chronic heart failure. N Engl J Med. 2001 May 31;344(22):1651-8. http://www.ncbi.nlm.nih.gov/pubmed/11386263

[lxviii] Carvedilol: McDonagh TA, Metra M, Adamo M, Gardner RS, Baumbach A, Böhm M, et al; ESC Scientific Document Group. 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. Eur Heart J. 2021 Sep 21;42(36):3599-3726. https://pubmed.ncbi.nlm.nih.gov/34447992/

[lxix] Digoxin: Fauchier L, Laborie G, Clementy N, Bernard A, Angoulvant D, Lip GHY, Babuty D. Effect of digoxin on all-cause mortality in patients with atrial fibrillation in a population-based cohort study. Heart Failure Congress; May 24, 2015; Seville, Spain.Presentation 539.https://www.escardio.org/

Digoxin:Rathore SS, Curtis JP, Wang Y, Bristow MR, Krumholz HM. Association of serum digoxin concentration and outcomes in patients with heart failure. *JAMA*. 2003 Feb 19;289(7):871-8. http://www.ncbi.nlm.nih.gov/pubmed/12588271

Digoxin: South African Medicines Formulary, 14th Edition. Division of Clinical Pharmacology. University of Cape Town, 2022.

[lxx] Vancomycin, IV: South African Medicines Formulary, 14th Edition. Division of Clinical Pharmacology. University of Cape Town, 2022.

[lxxi] Gentamicin, IV (dosing): Nicolau DP, Freeman CD, Belliveau PP, Nightingale CH, Ross JW, Quintiliani R. Experience with a once-daily aminoglycoside program administered to 2,184 adult patients. Antimicrob Agents Chemother. 1995 Mar;39(3):650-5. https://pubmed.ncbi.nlm.nih.gov/7793867/

Gentamicin, IV (dosing): Habib G, Lancellotti P, Antunes MJ, Bongiorni MG, Casalta JP, Del Zotti F, Dulgheru R, et al; ESC Scientific Document Group. 2015 ESC Guidelines for the management of infective endocarditis: The Task Force for the Management of Infective Endocarditis of the European Society of Cardiology (ESC). Endorsed by: European Association for Cardio-Thoracic Surgery (EACTS), the European Association of Nuclear Medicine (EANM). Eur Heart J. 2015 Nov 21;36(44):3075-3128. https://pubmed.ncbi.nlm.nih.gov/26320109/

[lxxii] Gentamicin, IV (dosing): Nicolau DP, Freeman CD, Belliveau PP, Nightingale CH, Ross JW, Quintiliani R. Experience with a once-daily aminoglycoside program administered to 2,184 adult patients. Antimicrob Agents Chemother. 1995 Mar;39(3):650-5. https://pubmed.ncbi.nlm.nih.gov/7793867/

Gentamicin, IV (dosing): Habib G, Lancellotti P, Antunes MJ, Bongiorni MG, Casalta JP, Del Zotti F, Dulgheru R, et al; ESC Scientific Document Group. 2015 ESC Guidelines for the management of infective endocarditis: The Task Force for the Management of Infective Endocarditis of the European Society of Cardiology (ESC). Endorsed by: European Association for Cardio-Thoracic Surgery (EACTS), the European Association of Nuclear Medicine (EANM). Eur Heart J. 2015 Nov 21;36(44):3075-3128. https://pubmed.ncbi.nlm.nih.gov/26320109/

[lxxiii] Empiric therapy (infective endocarditis): Habib G, Lancellotti P, Antunes MJ, Bongiorni MG, Casalta JP, Del Zotti F, Dulgheru R, et al; ESC Scientific Document Group. 2015 ESC Guidelines for the management of infective endocarditis: The Task Force for the Management of Infective Endocarditis of the European Society of Cardiology (ESC). Endorsed by: European Association for Cardio-Thoracic Surgery (EACTS), the European Association of Nuclear Medicine (EANM). Eur Heart J. 2015 Nov 21;36(44):3075-3128. https://pubmed.ncbi.nlm.nih.gov/26320109/

[lxxiv] Gentamicin, IV (dosing): Nicolau DP, Freeman CD, Belliveau PP, Nightingale CH, Ross JW, Quintiliani R. Experience with a once-daily aminoglycoside program administered to 2,184 adult patients. Antimicrob Agents Chemother. 1995 Mar;39(3):650-5. https://pubmed.ncbi.nlm.nih.gov/7793867/

Gentamicin, IV (dosing): Habib G, Lancellotti P, Antunes MJ, Bongiorni MG, Casalta JP, Del Zotti F, Dulgheru R, et al; ESC Scientific Document Group. 2015 ESC Guidelines for the management of infective endocarditis: The Task Force for the Management of Infective Endocarditis of the European Society of Cardiology (ESC). Endorsed by: European Association for Cardio-Thoracic Surgery (EACTS), the European Association of Nuclear Medicine (EANM). Eur Heart J. 2015 Nov 21;36(44):3075-3128. https://pubmed.ncbi.nlm.nih.gov/26320109/

[lxxv] Gentamicin, IV (dosing): Nicolau DP, Freeman CD, Belliveau PP, Nightingale CH, Ross JW, Quintiliani R. Experience with a once-daily aminoglycoside program administered to 2,184 adult patients. Antimicrob Agents Chemother. 1995 Mar;39(3):650-5. https://pubmed.ncbi.nlm.nih.gov/7793867/

Gentamicin, IV (dosing): Habib G, Lancellotti P, Antunes MJ, Bongiorni MG, Casalta JP, Del Zotti F, Dulgheru R, et al; ESC Scientific Document Group. 2015 ESC Guidelines for the management of infective endocarditis: The Task Force for the Management of Infective Endocarditis of the European Society of Cardiology (ESC). Endorsed by: European Association for Cardio-Thoracic Surgery (EACTS), the European Association of Nuclear Medicine (EANM). Eur Heart J. 2015 Nov 21;36(44):3075-3128. https://pubmed.ncbi.nlm.nih.gov/26320109/

[lxxvi] Gentamicin, IV (Enterococcal infective endocarditis): Nicolau DP, Freeman CD, Belliveau PP, Nightingale CH, Ross JW, Quintiliani R. Experience with a once-daily aminoglycoside program administered to 2,184 adult patients. Antimicrob Agents Chemother. 1995 Mar;39(3):650-5. https://pubmed.ncbi.nlm.nih.gov/7793867/

Gentamicin, IV (Enterococcal infective endocarditis): Habib G, Lancellotti P, Antunes MJ, Bongiorni MG, Casalta JP, Del Zotti F, Dulgheru R, et al; ESC Scientific Document Group. 2015 ESC Guidelines for the management of infective endocarditis: The Task Force for the Management of Infective Endocarditis of the European Society of Cardiology (ESC). Endorsed by: European Association for Cardio-Thoracic Surgery (EACTS), the European Association of Nuclear Medicine (EANM). Eur Heart J. 2015 Nov 21;36(44):3075-3128. https://pubmed.ncbi.nlm.nih.gov/26320109/

[lxxvii] Ceftriaxone, IV (Enterococcal infective endocarditis): Fernández-Hidalgo N, Almirante B, Gavaldà J, Gurgui M, Peña C, de Alarcón A, Ruiz J, et al. Ampicillin plus ceftriaxone is as effective as ampicillin plus gentamicin for treating enterococcus faecalis infective endocarditis. Clin Infect Dis. 2013 May;56(9):1261-8. https://pubmed.ncbi.nlm.nih.gov/23392394/

Ceftriaxone, IV (Enterococcal infective endocarditis): Habib G, Lancellotti P, Antunes MJ, Bongiorni MG, Casalta JP, Del Zotti F, Dulgheru R, et al; ESC Scientific Document Group. 2015 ESC Guidelines for the management of infective endocarditis: The Task Force for the Management of Infective Endocarditis of the European Society of Cardiology (ESC). Endorsed by: European Association for Cardio-Thoracic Surgery (EACTS), the European Association of Nuclear Medicine (EANM). Eur Heart J. 2015 Nov 21;36(44):3075-3128. https://pubmed.ncbi.nlm.nih.gov/26320109/

[lxxviii] Staphyloccal-cloxacillin-susceptible antimicrobial therapy Directed therapy infective endocarditis – native valves): Cosgrove SE, Vigliani GA, Fowler VG Jr, Abrutyn E, Corey GR, Levine DP, Rupp ME, et al. Initial low-dose gentamicin

for Staphylococcus aureus bacteremia and endocarditis is nephrotoxic. Clin Infect Dis 2009;48:713–721. https://pubmed.ncbi.nlm.nih.gov/19207079/

Staphyloccal-cloxacillin-susceptible antimicrobial therapy Directed therapy infective endocarditis – native valves): Habib G, Lancellotti P, Antunes MJ, Bongiorni MG, Casalta JP, Del Zotti F, Dulgheru R, et al; ESC Scientific Document Group. 2015 ESC Guidelines for the management of infective endocarditis: The Task Force for the Management of Infective Endocarditis of the European Society of Cardiology (ESC). Endorsed by: European Association for Cardio-Thoracic Surgery (EACTS), the European Association of Nuclear Medicine (EANM). Eur Heart J. 2015 Nov 21;36(44):3075-3128. https://pubmed.ncbi.nlm.nih.gov/26320109/

[lxxix] Directed therapy (infective endocarditis – native valves): Habib G, Lancellotti P, Antunes MJ, Bongiorni MG, Casalta JP, Del Zotti F, Dulgheru R, et al; ESC Scientific Document Group. 2015 ESC Guidelines for the management of infective endocarditis: The Task Force for the Management of Infective Endocarditis of the European Society of Cardiology (ESC). Endorsed by: European Association for Cardio-Thoracic Surgery (EACTS), the European Association of Nuclear Medicine (EANM). Eur Heart J. 2015 Nov 21;36(44):3075-3128. https://pubmed.ncbi.nlm.nih.gov/26320109/

[lxxx] Antibiotics for prophylaxis (infective endocardtis): NICE, Clinical guideline 64 Prophylaxis against infective endocarditis: antimicrobial prophylaxis against infective endocarditis in adults and children undergoing interventional procedures, March 2008. www.nice.org.uk/CG064

[lxxxi] Classification of hypertension (office-based): Unger T, Borghi C, Charchar F, Khan NA, Poulter NR, Prabhakaran D, et al. 2020 International Society of Hypertension global hypertension practice guidelines. J Hypertens. 2020 Jun;38(6):982-1004. https://pubmed.ncbi.nlm.nih.gov/32371787/

[lxxxii] Target BP for primary hypertension: Black A, Parrish AG, Rayner B, Leong TD, Mpongoshe V. Target blood pressure: a South African perspective. Cardiovasc J Afr. 2019 Mar/Apr;30(2):71-73. https://pubmed.ncbi.nlm.nih.gov/31155633/

Target BP for primary hypertension: Brunström M, Carlberg B. Association of Blood Pressure Lowering With Mortality and Cardiovascular Disease Across Blood Pressure Levels: A Systematic Review and Meta-analysis. JAMA Intern Med. 2018 Jan 1;178(1):28-36. https://pubmed.ncbi.nlm.nih.gov/29131895/

[lxxxiii] Algorithm for the stepwise treatment of hypertension without compelling indications: Unger T, Borghi C, Charchar F, Khan NA, Poulter NR, Prabhakaran D, et al. 2020 International Society of Hypertension global hypertension practice guidelines. J Hypertens. 2020 Jun;38(6):982-1004. https://pubmed.ncbi.nlm.nih.gov/32371787/

[lxxxiv] Ideal BMI: National Heart, Lung, and Blood Institute in cooperation with The National Institute of Diabetes and Digestive and Kidney Diseases. Clinical Guidelines on the Identification, Evaluation, and Treatment of Overweight and Obesity in Adults, September 1998. Report No.: 98-4083. https://www.ncbi.nlm.nih.gov/books/NBK2003/

[lxxxv] Antihypertensives – fixed dose combinations: Gupta P, Patel P, Štrauch B, Lai FY, Akbarov A, Marešová V, White CMJ, Petrák O, Gulsin GS, Patel V, Rosa J, Cole R, Zelinka T, Holaj R, Kinnell A, Smith PR, Thompson JR, Squire I, Widimský J Jr, Samani NJ, Williams B, Tomaszewski M. Risk Factors for Nonadherence to Antihypertensive Treatment. Hypertension. 2017 Jun;69(6):1113-1120. https://www.ncbi.nlm.nih.gov/pubmed/28461599

[lxxxvi] Suboptimal BP control – treatment inertia: Tiffe T, Wagner M, Rucker V, Morbach C, Gelbrich G, Stork S, Heuschmann PU. Control of cardiovascular risk factors and its determinants in the general population- findings from the STAAB cohort study. BMC Cardiovasc Disord 2017;17:276. https://www.ncbi.nlm.nih.gov/pubmed/29096615

Suboptimal BP control – treatment inertia: Berry KM, Parker WA, Mchiza ZJ, Sewpaul R, Labadarios D, Rosen S, Stokes A. Quantifying unmet need for hypertension care in South Africa through a care cascade: evidence from the SANHANES, 2011-2012. BMJ Glob Health. 2017 Aug 16;2(3):e000348. https://www.ncbi.nlm.nih.gov/pubmed/29082013

[lxxxvii] Hydrochlorothiazide, oral (skin cancer risk): Pedersen SA, Gaist D, Schmidt SAJ, Hölmich LR, Friis S, Pottegård A. Hydrochlorothiazide use and risk of nonmelanoma skin cancer: A nationwide case-control study from Denmark. J Am Acad Dermatol. 2018 Apr;78(4):673-681.e9. https://www.ncbi.nlm.nih.gov/pubmed/29217346

Hydrochlorothiazide, oral (skin cancer risk): Pottegård A, Hallas J, Olesen M, Svendsen MT, Habel LA, Friedman GD, Friis S. Hydrochlorothiazide use is strongly associated with risk of lip cancer. J Intern Med. 2017 Oct;282(4):322-331. https://www.ncbi.nlm.nih.gov/pubmed/28480532

Hydrochlorothiazide, oral (skin cancer risk): National Department of Health, Essential Drugs Programme: Updated Notice: Risk of skin cancer associated with hydrochlorothiazide, 6 March 2019. https://www.knowledgehub.org.za/content/standard-treatment-guidelines-and-essential-medicines-list

Hydrochlorothiazide, oral (first-line therapy): National Department of Health, Affordable Medicines, EDP-PHC and Adult Hospital level. Medicine Review: Indapamide compared to hydrochlorothiazide as first-line therapy for hypertension in adults, 16 July 2021. https://www.knowledgehub.org.za/content/standard-treatment-guidelines-and-essential-medicines-list

[lxxxviii] Calcium channel blocker (place in treatment protocol): Brewster LM, van Montfrans GA, Oehlers GP, Seedat YK. Systematic review:antihypertensive drug therapy in patients of African and South Asian ethnicity. Intern Emerg Med. 2016 Apr;11(3):355-74. https://www.ncbi.nlm.nih.gov/pubmed/27026378

Calcium channel blocker (dosing at bedtime): Hermida RC, Crespo JJ, Domínguez-Sardiña M, Otero A, Moyá A, Ríos MT, Sineiro E, Castiñeira MC, Callejas PA, Pousa L, Salgado JL, Durán C, Sánchez JJ, Fernández JR, Mojón A,

Ayala DE; Hygia Project Investigators. Bedtime hypertension treatment improves cardiovascular risk reduction: the Hygia Chronotherapy Trial. Eur Heart J. 2019 Oct 22. pii: ehz754. https://www.ncbi.nlm.nih.gov/pubmed/31641769

lxxxix Enalapril, oral (daily dosing): Girvin B, McDermott BJ, Johnston GD. A comparison of enalapril 20 mg once daily versus 10 mg twice daily in terms of blood pressure lowering and patient compliance. J Hypertens. 1999 Nov;17(11):1627-31. https://www.ncbi.nlm.nih.gov/pubmed/10608477

Enalapril, oral (daily dosing): Davies RO, Gomez HJ, Irvin JD, Walker JF. An overview of the clinical pharmacology of enalapril. Br J Clin Pharmacol. 1984;18 Suppl 2:215S-229S. https://www.ncbi.nlm.nih.gov/pubmed/6099737

Enalapril, oral (dosing at bedtime): Hermida RC, Crespo JJ, Domínguez-Sardiña M, Otero A, Moyá A, Ríos MT, Sineiro E, Castiñeira MC, Callejas PA, Pousa L, Salgado JL, Durán C, Sánchez JJ, Fernández JR, Mojón A, Ayala DE; Hygia Project Investigators. Bedtime hypertension treatment improves cardiovascular risk reduction: the Hygia Chronotherapy Trial. Eur Heart J. 2019 Oct 22. pii: ehz754. https://www.ncbi.nlm.nih.gov/pubmed/31641769

xc Spironolactone, oral: Williams B, MacDonald TM, Morant S, Webb DJ, Sever P, McInnes G, Ford I, et al.; British Hypertension Society's PATHWAY Studies Group. Spironolactone versus placebo, bisoprolol, and doxazosin to determine the optimal treatment for drug-resistant hypertension (PATHWAY-2): a randomised, double-blind, crossover trial. Lancet. 2015 Nov 21;386(10008):2059-68. http://www.ncbi.nlm.nih.gov/pubmed/26414968

xci Beta-blocker, oral (dosing at bedtime): Hermida RC, Crespo JJ, Domínguez-Sardiña M, Otero A, Moyá A, Ríos MT, Sineiro E, et al.; Hygia Project Investigators. Bedtime hypertension treatment improves cardiovascular risk reduction: the Hygia Chronotherapy Trial. Eur Heart J. 2019 Oct 22. pii: ehz754. https://www.ncbi.nlm.nih.gov/pubmed/31641769

xcii Lidocaine 1%: Amir J, Ginat S, Cohen YH, Marcus TE, Keller N, Varsano I. Lidocaine as a diluent for administration of benzathine penicillin G. Pediatr Infect Dis J. 1998 Oct;17(10):890-3. http://www.ncbi.nlm.nih.gov/pubmed/9802630

xciii Amoxicillin, oral (adults): Brink AJ, Cotton M, Feldman C, Finlayson H, Friedman R, Green R, Hendson W, Hockman M, Maartens G, Madhi S, Reubenson G, Silverbauer E, Zietsman I. Updated recommendations for the management of upper respiratory tract infections in South Africa. S Afr Med J. 2015 Apr 6;105(5):344-52. http://www.ncbi.nlm.nih.gov/pubmed/26242659

Amoxicillin, oral (adults): National Department of Health: Affordable Medicines, EDP-Primary Health Care level. Medicine Review: Phenoxymethylpenicillin vs amoxicillin for tonsilitis_pharyngitis, October 2016. https://www.knowledgehub.org.za/content/standard-treatment-guidelines-and-essential-medicines-list

xciv Azithromycin: van Driel ML, De Sutter AI, Keber N, Habraken H, Christiaens T. Different antibiotic treatments for group A streptococcal pharyngitis. Cochrane Database Syst Rev. 2013 Apr 30;4:CD004406. http://www.ncbi.nlm.nih.gov/pubmed/23633318

Azithromycin: South African Medicines Formulary, 14th Edition. Division of Clinical Pharmacology. University of Cape Town, 2022.

Azithromycin: Guo D, Cai Y, Chai D, Liang B, Bai N, Wang R. The cardiotoxicity of macrolides: a systematic review.Pharmazie. 2010 Sep;65(9):631-40. Review.http://www.ncbi.nlm.nih.gov/pubmed/21038838/

xcv Period of antibiotic prophylaxis therapy:Begs S, Petrson G, Thompson A. Report for the 2nd meeting of the World Health Organization's subcommittee of the Expert Committee of the selection and use of essential medicines: Antibiotic use for the prevention and treatment of rheumatic fever and treatment of rheumatic fever and rheumatic heart disease in children. 30 June 2008.
http://www.who.int/selection_medicines/committees/subcommittee/2/RheumaticFever_review.pdf

Period of antibiotic prophylaxis therapy: Gerber MA, Baltimore RS, Eaton CB, Gewitz M, Rowley AH, Shulman ST, Taubert KA. Prevention of rheumatic fever and diagnosis and treatment of acute Streptococcal pharyngitis: a scientific statement from the American Heart Association Rheumatic Fever, Endocarditis, and Kawasaki Disease Committee of the Council on Cardiovascular Disease in the Young, the Interdisciplinary Council on Functional Genomics and Translational Biology, and the Interdisciplinary Council on Quality of Care and Outcomes Research: endorsed by the American Academy of Pediatrics. Circulation. 2009 Mar 24;119(11):1541-51.
http://www.ncbi.nlm.nih.gov/pubmed/19246689

xcvi Lidocaine 1%: Amir J, Ginat S, Cohen YH, Marcus TE, Keller N, Varsano I. Lidocaine as a diluent for administration of benzathine penicillin G. Pediatr Infect Dis J. 1998 Oct;17(10):890-3. http://www.ncbi.nlm.nih.gov/pubmed/9802630

CHAPTER 4

DERMATOLOGY

Extemporaneous compounding of some of the preparations listed should only take place at institutions where the competencies and equipment are available.

4.1 ACNE

L70.0-5/L70.8-9

DESCRIPTION

Acne is an inflammatory condition of the pilosebaceous unit. Secondary changes can lead to scarring and pigmentation.

Mild acne:
Predominantly consists of non-inflammatory comedones.

Moderate acne:
Consists of a mixture of non-inflammatory comedones and inflammatory papules and pustules.

Severe acne:
Characterised by the presence of widespread nodules and cysts, as well as a preponderance of inflammatory papules and pustules.

GENERAL MEASURES

» Do not squeeze lesions.
» Avoid greasy or oily topical products such as moisturisers that block the hair follicle openings.
» Discourage excessive facial washing.

MEDICINE TREATMENT

For the primary management of acne, see Primary Health Care Standard Treatment Guidelines and Essential Medicine List, Section 5.3: Acne vulgaris.

Women who have inflammatory acne and also require oral contraception can be initiated on a cyproterone acetate-containing combined oral contraceptive pill, provided that they have no personal or family history of breast cancer or venous thrombosis.

- Cyproterone acetate 2 mg plus ethinyl estradiol 35 mcg, oral daily.

LoE:Ia[i]

Note: Discuss all severe cases with a dermatologist.

4.2 CELLULITIS AND ERYSIPELAS

L03.0-3/L03.8-9 + (L04.0-3/L04.8-9/B95.0-8) and A46

DESCRIPTION

These are skin and subcutaneous infections with pain, swelling, and erythema, usually caused by streptococci and staphylococci, and occasionally other organisms. Regional lymphadenitis may be present. Erysipelas has a raised demarcated border, whilst the border is indistinct in cellulitis.

The presence of areas of necrosis, haemorrhage, or pain out of proportion to the physical signs should raise suspicion of necrotising fasciitis which requires aggressive surgical debridement and broad-spectrum antibiotics (e.g. amoxicillin/clavulanic acid) as these infections are often polymicrobial.

GENERAL MEASURES

» Elevate the affected limb to reduce swelling and pain.
» Hydrate.

MEDICINE TREATMENT

Non-severe infection
Antibiotic therapy:

- Cefalexin, oral, 500 mg 6 hourly for 5 days. A

OR

- Flucloxacillin, oral, 500 mg 6 hourly for 5 days. A

LoE:IVb[ii]

Severe penicillin allergy: (Z88.0)

- Macrolide, e.g.:
- Azithromycin, oral, 500 mg daily for 3 days. W

Note: Severe cases may require parenteral antibiotics.

Severe infection
The recommended duration of antimicrobial therapy is 5 days, but treatment should be extended if the infection has not improved within this time period.

LoE:IIIb[iii]

- Cefazolin, IV, 1 g 8 hourly. A

When there is clinical improvement, change to: LoE:IIIb[iv]

- Flucloxacillin, oral, 500 mg 6 hourly. A

Severe penicillin allergy: (Z88.0)

- Clindamycin, IV, 600 mg 8 hourly. A

When there is clinical improvement, change to:

- Clindamycin, oral, 450 mg 8 hourly. A

Note:

» If patients are treated with intravenous antibiotics, they should be switched to oral agents as soon as there is clinical improvement.

» Intravenous antibiotics are preferred in the setting of rapid progression of erythema.

Pain control:

- NSAID, oral: e.g.
- Ibuprofen, oral, 400 mg 8 hourly with meals.

OR

- Paracetamol, oral, 500 mg–1 g, 4–6 hourly as required (to a maximum of 4 g in 24 hours).
  - Maximum dose: 15 mg/kg/dose.

Note:

» If the patient is admitted and bed-bound with lower limb cellulitis, consider deep venous thrombosis prophylaxis. (See Section 2.8:Venous thrombo-embolism.)

» If Tinea pedis is suspected to be the predisposing cause, treat accordingly. See Section 4.10: Fungal infections.

REFERRAL

Urgent

» For debridement if necrotising fasciitis is suspected, i.e. gangrene, gas in the tissues or haemorrhagic bullae.

Non-urgent

» To surgeon for non-response.

» For further investigation and potential biopsy if cellulitis is associated with wounds exposed to aquatic environments**,** (salt water, brackish water, or fresh water), or if there is a lack of response to treatment.

4.3 IMPETIGO

L01.0-1A + (B95.0-8)

DESCRIPTION

Superficial skin infection, starting as vesicles with an inflammatory halo. Later a characteristic honey-coloured crust on erythematous base develops which heals without scarring. Usually caused by group A streptococci or staphylococci. Post-streptococcal glomerulonephritis is a potential complication.

GENERAL MEASURES

» Good personal and household hygiene to reduce carriage of organisms and spread of infection.
» Wash and soak lesions in soapy water to soften and remove crusts.

MEDICINE TREATMENT

Antibiotic therapy

- Flucloxacillin, oral, 500 mg 6 hourly for 5 days. A

Severe penicillin allergy: (Z88.0)

- Macrolide, e.g.:
- Azithromycin, oral, 500 mg daily for 3 days. W

4.4 FURUNCLES AND ABSCESSES

L02.0-4/L02.8-9/H00.0/H60.0/N76.4/J34.0 + (B95.6-8)

DESCRIPTION

Localised bacterial skin infection of hair follicles (furuncle/boil) or dermis (abscess), usually with *S. aureus*.
The surrounding skin becomes:

» swollen
» hot
» red
» tender to touch.

Note:

» Boils in diabetic, malnourished, or other immunocompromised patients are more likely to develop complications.
» Check blood glucose levels and HIV status if the boils are recurrent.

GENERAL MEASURES

Treatment will depend on the abscess size:

» Small furuncles should be managed with a moist, warm compress applied to the infected area, several times per day to promote drainage.
» Large fluctuant lesions should be treated with incision and drainage.

The following sites should be drained by a surgeon:

» Peri-rectal abscess.
» Anterior and lateral neck abscess.
» Abscess adjacent to nerves or blood vessels e.g. carotid artery, facial nerve, central triangle of face (formed by the corners of the mouth and the nasal bridge).

Note:

» Needle aspiration is insufficient for adequate abscess drainage.
» Systemic antibiotics are used only as indicated below.

MEDICINE TREATMENT

Antibiotic therapy

Systemic antibiotics are seldom necessary, except for facial abscesses, or abscesses associated with tender draining lymph nodes, fever, or extensive surrounding cellulitis.

Antibiotics should usually be given for 5–10 days, depending on clinical response.

- Cefazolin, IV, 1g 8 hourly. A

LoE:IIIb[v]

When there is clinical improvement, change to:

- Flucloxacillin, oral, 500 mg 6 hourly. A

Severe penicillin allergy: (Z88.0)

- Clindamycin, IV, 600 mg 8 hourly. A

When there is clinical improvement, change to:

- Clindamycin, oral, 450 mg 8 hourly. A

4.5 ATOPIC ECZEMA/ DERMATITIS

L20.0/L20.8-9

DESCRIPTION

Eczema is a pruritic, inflammatory skin condition characterised by vesicles, weeping, and crusting in the acute phase; and thickened, scaly skin with increased skin markings known as lichenification in the chronic phase.

Assessing severity

1% of body surface is equal to the size of one hand (including the fingers) of the patient.

Mild

» Less than 5% body surface involved.
» No acute changes.
» No significant impact on quality of life.

Moderate

» 5–30% body surface involved.
» Mild dermatitis with acute changes.
» Mild dermatitis with significant impact on quality of life.

Severe

» More than 30% body surface involved.
» Moderate dermatitis with acute changes.
» Moderate dermatitis with significant impact on quality of life.

GENERAL MEASURES

» Avoid exposure to trigger or precipitating factors, where applicable.
» Avoid irritants such as strong detergents, antiseptics, foam (especially hot) baths, soaps, and rough occlusive clothing (silk is better than cotton, which is better than nylon, which is better than wool).
» Good personal hygiene with once daily washing to remove crusts and accretions and avoid secondary infection.
» Keep fingernails short to minimise trauma from scratching.
» Respect patient preference for cream or ointment topical treatment.
» Wet wraps may help control eczema and pruritus but should not be used for infected eczema.
» Diet modification has no role in atopic eczema treatment unless double blind challenge testing proves food sensitivity.
» Avoid smoking.

LoE:IIIb[vi]

MEDICINE TREATMENT

To relieve skin dryness:

- Aqueous cream topical, to wash or bath.

AND

- Emulsifying ointment (UE), topical, applied daily to dry areas as a moisturiser.

LoE:IIIb[vii]

Note:
Maintenance treatment with moisturising soap, creams, and ointments as described above should be continued, even if the dermatitis is controlled.

To control wet or weepy dermatitis:
Creams are preferred to ointments on open or oozing lesions and in intertriginous folds.

Mild eczema

- Hydrocortisone 1%, topical, applied 12 hourly to body and face until control is achieved.
  - Can be used on face and in skin folds.
  - Apply sparingly to the face.
  - Use with caution around the eyes.

Moderate and severe eczema

- Potent topical corticosteroids, e.g.:
- Betamethasone 0.1%, topical, applied daily for 7 days to the affected areas.
  - Apply sparingly to face, neck and flexures.

Note: There is no clear benefit for more than once daily application.

LoE:Ia[viii]

If non-responsive:
Refer for dermatologist opinion, and whilst awaiting referral, initiate:
- Prednisone, oral, 0.5 mg/kg daily, for ≤ 2 weeks. (Specialist initiated.)

Maintenance therapy
Once eczema is controlled, wean to the lowest potency topical corticosteroid that maintains remission and continue applying twice a week.

- Emulsifying ointment (UE), topical, applied daily.
  - Apply moisturiser as needed.

Infected eczema
This is usually due to staphylococcal infection.

Antibiotic therapy
- Flucloxacillin, oral, 500 mg 6 hourly for 5 days. A

Severe penicillin allergy: (Z88.0)
- Clindamycin, oral, 450 mg 8 hourly for 5 days. A

For sedation and relief of itch:
- Chlorphenamine, oral, 4 mg at night as needed.

Eczema herpeticum (B00.0)
Therapy should be initiated without delay:
- Aciclovir, oral, 400 mg 8 hourly for 7 days.

LoE:IIIb[ix]

If patient is unable to swallow due to odynophagia:
- Aciclovir, IV, 5 mg/kg/dose, 8 hourly for 7 days.
  - Infuse over 1 hour.

LoE:IIIb[x]

REFERRAL
» Severe, non-responsive, or complicated cases.
» Cases with uncertain diagnosis (e.g. severe infection including disseminated herpes simplex).

4.6 ERYTHEMA MULTIFORME, STEVENS JOHNSON SYNDROME, TOXIC EPIDERMAL NECROLYSIS
L51.0-2/L51.8-9

DESCRIPTION
Erythema multiforme
An acute, self-limiting, and commonly recurrent inflammatory skin eruption with variable involvement of the mucous membranes, and without systemic symptoms.

Symmetrically distributed crops of target lesions (dark centre, an inner, pale ring surrounded by an outer red ring) often involving palms and soles are characteristic. This condition is usually due to an infection, commonly herpes simplex or mycoplasma.

Stevens-Johnson Syndrome (SJS) and Toxic Epidermal Necrolysis (TEN)

Life-threatening acute hypersensitivity reactions with systemic upset, epidermal necrosis, and mucous membrane involvement. TEN and SJS are different ends of the same spectrum: in SJS, the involvement is <10%, while in TEN, epidermal necrosis involves >30% of body surface area. Non-specific prodromal symptoms, often mistaken as an upper respiratory tract infection, may occur before skin lesions become apparent.

Cutaneous lesions may start as a dusky red macular rash, progressing to confluence with epidermal necrosis and large, flaccid blisters which rupture, leaving large areas of denuded skin. Mucous membrane erosions are common and multi-organ involvement may be present.

This condition is usually due to medication, e.g. sulfonamides, non-nucleoside reverse transcriptase inhibitors (especially nevirapine), anti-epileptics (phenytoin, phenobarbitone, carbamazepine, lamotrigine), allopurinol, and laxatives (phenolphthalein).

Complications include:

» Dehydration, electrolyte disturbances, and shock.
» Hypoalbuminaemia.
» Hypo- and more commonly hyperthermia.
» High output cardiac failure.
» Secondary infection and sepsis.
» Adhesions and scarring.

Stop all medicines, where safely possible, including complementary, alternative, and self-medication.

GENERAL MEASURES

Immediate in hospital evaluation

» The foundation of management is supportive care, good nursing, and the prevention of dehydration and sepsis.
» Stop all potentially implicated medicines.
» Patients usually require care in a high or intensive care unit with dedicated nursing.
» Attempt to identify causative agent as early withdrawal of agent improves prognosis.

Monitoring
» Monitor vital organ function.
» Examine daily for infection and swab infected lesions. Do blood cultures if fever persists or suspicion of infection.

Dressings
Ensure skin hygiene routines with daily cleansing and bland, non-adherent dressings as needed.

Do not use silver sulfadiazine if SJS/TEN is thought to be due to co-trimoxazole or other sulfonamides.

Mucous membranes:
» Regular supervised oral, genital, and eye care to prevent adhesions and scarring.
» Two-hourly mouth washes with bland mouth wash, e.g. glycothymol.
» Examine daily for ocular lesions and treat 2-hourly with eye care and lubricants (see Section 18.9: Dry eye) and break down adhesions.
» Treat genitalia 6-hourly with Sitz baths and encourage movement of opposing eroded surfaces to prevent adhesions.

Fluids:
» Oral rehydration is preferred but intravenous fluid therapy may be required to treat significant dehydration.
» Encourage oral fluids to prevent pharyngeal adhesions.
» Provide soft, lukewarm food. Restrict nasogastric feeds to those patients that are unable to eat, as they may lead to additional trauma with bleeding, secondary infection, and adhesions.

Note: All patients should receive a notification bracelet/necklace on discharge.

MEDICINE TREATMENT

Corticosteroids
The use of systemic corticosteroids is not supported by evidence and is therefore not recommended.

Antibiotic therapy
» Systemic antibiotics may be indicated, depending on results of appropriate cultures. They should not be administered routinely, nor be given prophylactically.
» Organisms identified on skin swabs are not a good indicator of systemic infection.

Analgesia
Appropriate and adequate analgesia for pain should be given at least half an hour before dressing changes. (See Section 12.4.1: Perioperative analgesics.)

REFERRAL/CONSULTATION

» Discuss with a specialist, if considering re-initiation of medication.
» Consult a specialist immediately where there is ocular involvement.

4.7 LEG ULCERS, COMPLICATED

L97

DESCRIPTION

A chronic, relapsing disorder of the lower limbs. It has many causes and is often associated with lipodermatosclerosis (bound-down, fibrosed skin) and eczema. It is mainly associated with vascular (predominantly venous) insufficiency and immobility. It is also associated with neuropathy, and, occasionally, with infections, neoplasia, trauma, or other rare conditions.

GENERAL MEASURES

» The aim of management should be to:
  – Treat underlying conditions, e.g. heart failure, diabetes mellitus, and venous stasis.
  – Limit the extent of damage.
  – Encourage rapid healing to minimise scarring and fibrosis.
  – Prevent recurrences.
» Avoid all topical irritants and allergens, e.g. lanolin, neomycin, bacitracin, parabens, fusidic acid, clioquinol, antihistamine creams, etc.
» If the ulcer is oedema- or stasis-related, rest the leg in an elevated position.
» In venous insufficiency, compression (bandages or stockings) is essential to achieve and maintain healing, provided the arterial supply is normal.
» In patients with arterial insufficiency, avoid pressure elevation and compression bandages or stockings on bony prominences and the toes.
» Counsel the patient on meticulous foot care and avoidance of minor trauma.
» Encourage walking and exercise.
» Encourage patients with neuropathy not to walk barefoot, to check their shoes for foreign objects, examine their feet daily for trauma, and to test bath water before bathing to prevent getting burnt.
» Avoid excessive local heat.
» Indications for surgical procedures include:
  – slough removal
  – arterial insufficiency
  – surgery for varicose veins
  – skin grafting

MEDICINE TREATMENT

Antibiotic therapy

Systemic antibiotics are seldom required for ulcers and should be considered only if there is surrounding cellulitis. These infections are typically polymicrobial and broad-spectrum antibiotics are recommended.

- Amoxicillin/clavulanic acid, oral, 875/125 mg 12 hourly for 7 days.

Local wound care

Topical cleansing

Use bland, non-toxic products to clean the ulcer and surrounding skin.

For clean uninfected wounds:

- Sodium chloride 0.9% or sterile water.

Dress frequently with:

- Moistened dressing, e.g. gauze with sodium chloride 0.9%. *LoE:IIIb*[xi]

For exudative, infected wounds:

- Povidone-iodine 5% cream, topical, apply daily.

4.8 PSORIASIS

L40.0-5/L40.8-9

DESCRIPTION

This is an inflammatory condition of the skin and joints of unknown aetiology. Scaly, red papules and plaques over extensor surfaces and on the scalp are common. The nails and skin folds are often involved. In exceptional cases, it is localised to palms and soles and pustular skin lesions are seen, especially following rapid treatment withdrawal, e.g. steroids or systemic agents.

GENERAL MEASURES

» Counsel regarding precipitating factors and chronicity.
» Encourage sun exposure as tolerated.

MEDICINE TREATMENT

Local plaques

Maintenance therapy:

- Coal tar 5%, topical, apply at night.
  - Avoid use on the face, flexures, and genitalia.

For flares:

- Potent topical corticosteroids, e.g.: *LoE:IVb*[xii]
- Betamethasone 0.1%, topical, apply 12 hourly.
  - Decrease according to severity, reduce to hydrocortisone 1% cream, then stop.

Scalp psoriasis

Maintenance therapy:

- Wash with coal tar containing shampoo.

OR

- Coal tar 1%, topical, apply at night, under occlusion, and wash out the next morning.

For flares:

- Potent topical corticosteroids, e.g.: LoE:IVb[xiii]
- Betamethasone 0.1% lotion, topical, apply once daily.

Note:

» Avoid systemic corticosteroids.
» Patient adherence is the greatest barrier to treatment success with topical therapies.

REFERRAL

» Inadequate response to topical treatment.
» Severe disease, especially if there is joint involvement.

4.9 URTICARIA

L50.0-6/L50.8-9

DESCRIPTION

A transient itchy inflammatory skin and mucosal condition recognised by a wheal and flare reaction. There are many causes, and in most chronic cases, the precipitant for the urticaria is never found. Lesions due to insect bites are often grouped, show a central bite mark, are on exposed areas of the body, and are often associated with excoriation, vesicles, pigmentary changes, and secondary infection.

GENERAL MEASURES

» Limit exposure to triggers such as non-immune mast cell degranulators which aggravate and prolong urticaria, e.g. opioids (such as codeine), NSAIDs, salicylates, alcohol, etc.
» Avoid oral corticosteroids.

MEDICINE TREATMENT

Antihistamines

Regular use is recommended until the urticaria is quiescent.

For chronic urticaria, less sedating antihistamines are preferable:

- Cetirizine, oral, 10 mg daily.

REFERRAL
All patients with urticaria that have individual lesions for longer than 48 hours should be referred to a specialist to exclude urticarial vasculitis.

4.9.1 PAPULAR URTICARIA
L50.8

DESCRIPTION
Papular urticaria is a hypersensitivity disorder to insect bites, resulting in recurrent, and sometimes chronic, itchy papules on exposed areas of the body. An initial lesion appears, usually as a red papule, which may blister, become excoriated, and then heal with hyperpigmentation. Lesions usually occur in crops over several months. Chronic, severe, persistent reactions may be seen in immunocompromised patients, e.g. HIV infection, immunosuppressive therapy, and malnutrition.

GENERAL MEASURES
» Reduce exposure to insects by treating pets, using mosquito nets, and fumigating the household regularly.
» Use of insect repellents may be helpful.
» Examine carefully for burrows to rule out scabies.

MEDICINE TREATMENT
New inflamed lesions:
- Potent topical corticosteroids, e.g.: *LoE:IVb*[xiv]
- Betamethasone 0.1%, topical, apply daily for 5 days.

For sedation and relief of itch:
- Chlorphenamine, oral, 4 mg at night as needed in severe cases.

REFERRAL
Non-responsive and chronic cases.

4.10 FUNGAL INFECTIONS
B35.0-6/B35.8-9/B36.0-3/B36.8-9/B40.3/B45.2/B46.3

DESCRIPTION
The skin may be infected by fungi, and the clinical presentation varies with organism, body site infected, and the body's response to the infection.

GENERAL MEASURES
» Manage predisposing factors, e.g. occlusion, maceration, and underlying conditions such as diabetes mellitus, eczema, immunocompromising conditions, etc.

» Advise patient regarding spread of infection and exposure in communal, shared facilities (especially spread of dermatophytes).

MEDICINE TREATMENT

Yeast and dermatophytes (fungal infection of the skin):
- Imidazole, e.g.:
- Clotrimazole 1%, topical, apply 8 hourly until clear of disease (i.e. for at least 2 weeks after the lesions have cleared).

Pityriasis versicolor: (B36.0)
- Selenium sulfide 2.5% suspension, applied once weekly to all affected areas.
  - Allow to dry and leave overnight before rinsing off.
  - Repeat for 3 weeks.

Systemic antifungal therapy
Topical treatment is generally ineffective for dermatophyte hair and nail infections.
Systemic therapy may be indicated for immunocompromised individuals with extensive skin infection.
- Fluconazole, oral, 200 mg once weekly for 6 weeks.
  - For onychomycosis, 200 mg weekly for 6 months.

LoE:IIIb[xv]

Note: Recurrent infections may occur if repeat exposure is not prevented.

REFERRAL
» Non-responsive infections.
» Systemic infections.

4.11 VIRAL INFECTIONS

4.11.1 VIRAL WARTS/ANOGENITAL WARTS
B07/A63.0

DESCRIPTION
Superficial muco-cutaneous infection caused by the human papilloma virus.

GENERAL MEASURES
Patients with anogenital warts are at an increased risk of other STIs.

If the patient has anogenital warts:
» Pap smear should be offered to women to screen for cervical pathology.
» Screen for HIV and other STIs.

MEDICINE TREATMENT

Cutaneous warts

Treatment is seldom indicated.

Anogenital warts

- Podophyllotoxin 0.5% solution (patient application).
  - Wash the affected areas with soap and water, and dry thoroughly with your own towel.
  - Apply petroleum jelly to surrounding skin and mucous membranes for protection.
  - Apply podophyllotoxin 12 hourly for 3 consecutive days until lesions disappear.
  - Treatment may be repeated at weekly intervals for a total of four 3-day treatment courses if necessary.

OR

- Podophyllin 20% in compound benzoin tincture, topical (health care professional application).
  - Apply petroleum jelly to surrounding skin and mucous membrane for protection.
  - Apply at weekly intervals until lesions disappear.
  - Wash the solution off after 4 hours.

LoE:IIb[xvi]

Note:

» Podophyllin and podophyllotoxin are cytotoxic agents.
» Avoid systemic absorption.

CAUTION - Podophyllotoxin
Podophyllotoxin containing agents are contraindicated in pregnancy.

REFERRAL

» Extensive or recurrent anogenital warts.

4.11.2 SHINGLES (HERPES ZOSTER)

See Section 9.13: Zoster (shingles).

References:

[i] Cyproterone acetate 2 mg plus Ethinyl Estradiol 35 µg, oral: Arowojolu AO, Gallo MF, Lopez LM, Grimes DA. Combined oral contraceptive pills for treatment of acne. Cochrane Database Syst Rev. 2012 Jul 11;7:CD004425. http://www.ncbi.nlm.nih.gov/pubmed/22786490

Cyproterone acetate 2 mg plus Ethinyl Estradiol 35 µg, oral South African Medicines Formulary, 14th Edition. Division of Clinical Pharmacology. University of Cape Town, 2022.

[ii] Cephalexin: National Department of Health: Affordable Medicines, EDP- Primary Healthcare and Adult Hospital Level. Medicine Review: Evidence summary of the use of cephalexin for S Aureus skin infections, September 2022.

[iii] Intravenous antibiotics (severe cellulitis and erysipelas): Stevens DL, Bisno AL, Chambers HF, Dellinger EP, Goldstein EJ, Gorbach SL, Hirschmann JV, Kaplan SL, Montoya JG, Wade JC; Infectious Diseases Society of America. Practice guidelines for the diagnosis and management of skin and soft tissue infections: 2014 update by the Infectious Diseases Society of America. Clin Infect Dis. 2014 Jul 15;59(2):e10-52. https://www.idsociety.org/practice-guideline/skin-and-soft-tissue-infections/

[iv] Cefazolin, IV: Loubet P, Burdet C, Vindrios W, Grall N, Wolff M, Yazdanpanah Y, AndremontA, Duval X, Lescure FX. Cefazolin versus anti-staphylococcal penicillins for treatment of methicillin-susceptible Staphylococcus aureus bacteraemia: a narrative review. ClinMicrobiol Infect. 2017 Jul 8.pii: S1198-743X(17)30358-0.https://www.ncbi.nlm.nih.gov/pubmed/28698037

Cefazolin, IV: Bai AD, Showler A, Burry L, Steinberg M, Ricciuto DR, Fernandes T, Chiu A, Raybardhan S, Science M, Fernando E, Tomlinson G, Bell CM, Morris AM. Comparative effectiveness of cefazolin versus cloxacillin as definitive antibiotic therapy for MSSA bacteraemia: results from a large multicentre cohort study. J Antimicrob Chemother. 2015 May;70(5):1539-46. https://www.ncbi.nlm.nih.gov/pubmed/25614044

Cefazolin, IV: Perovic O, Singh-Moodley A, Govender NP, Kularatne R, Whitelaw A, Chibabhai V, Naicker P, Mbelle N, Lekalakala R, Quan V, Samuel C, Van Schalkwyk E; for GERMS-SA. A small proportion of community-associated methicillin-resistant Staphylococcus aureus bacteraemia, compared to healthcare-associated cases, in two South African provinces. Eur J Clin Microbiol Infect Dis. 2017 Dec;36(12):2519-2532. https://www.ncbi.nlm.nih.gov/pubmed/28849285

Cefazolin, IV: Stevens DL, Bisno AL, Chambers HF, Dellinger EP, Goldstein EJ, Gorbach SL, Hirschmann JV, Kaplan SL, Montoya JG, Wade JC; Infectious Diseases Society of America. Practice guidelines for the diagnosis and management of skin and soft tissue infections: 2014 update by the Infectious Diseases Society of America. Clin Infect Dis. 2014 Jul 15;59(2):e10-52. https://www.ncbi.nlm.nih.gov/pubmed/24973422

[v] Cefazolin, IV: Bai AD, Showler A, Burry L, Steinberg M, Ricciuto DR, Fernandes T, Chiu A, Raybardhan S, Science M, Fernando E, Tomlinson G, Bell CM, Morris AM. Comparative effectiveness of cefazolin versus cloxacillin as definitive antibiotic therapy for MSSA bacteraemia: results from a large multicentre cohort study. J Antimicrob Chemother. 2015 May;70(5):1539-46. https://www.ncbi.nlm.nih.gov/pubmed/25614044

Cefazolin, IV: Perovic O, Singh-Moodley A, Govender NP, Kularatne R, Whitelaw A, Chibabhai V, Naicker P, Mbelle N, Lekalakala R, Quan V, Samuel C, Van Schalkwyk E; for GERMS-SA. A small proportion of community-associated methicillin-resistant Staphylococcus aureus bacteraemia, compared to healthcare-associated cases, in two South African provinces. Eur J Clin Microbiol Infect Dis. 2017 Dec;36(12):2519-2532. https://www.ncbi.nlm.nih.gov/pubmed/28849285

Cefazolin, IV: Loubet P, Burdet C, Vindrios W, Grall N, Wolff M, Yazdanpanah Y, AndremontA, Duval X, Lescure FX. Cefazolin versus anti-staphylococcal penicillins for treatment of methicillin-susceptible Staphylococcus aureus bacteraemia: a narrative review. ClinMicrobiol Infect. 2017 Jul 8.pii: S1198-743X(17)30358-0.https://www.ncbi.nlm.nih.gov/pubmed/28698037

Cefazolin, IV: Stevens DL, Bisno AL, Chambers HF, Dellinger EP, Goldstein EJ, Gorbach SL, Hirschmann JV, Kaplan SL, Montoya JG, Wade JC; Infectious Diseases Society of America. Practice guidelines for the diagnosis and management of skin and soft tissue infections: 2014 update by the Infectious Diseases Society of America. Clin Infect Dis. 2014 Jul 15;59(2):e10-52. https://www.ncbi.nlm.nih.gov/pubmed/24973422

[vi] Sørensen JA, Clemmensen KK, Nixon RL, Diepgen TL, Agner T. Tobacco smoking and hand eczema - is there an association? Contact Dermatitis. 2015 Dec;73(6):326-35. https://pubmed.ncbi.nlm.nih.gov/26140658/

[vii] Aqueous cream and emollients: Tsang M, Guy RH. Effect of aqueous cream BP on human stratum corneum in vivo. *Br J Dermatol* 2010; 163:954–8.http://www.ncbi.nlm.nih.gov/pubmed/20649794

Aqueous cream and emollients: Mohammed D, Matts PJ, Hadgraft J, Lane ME. Influence of aqueous cream BP on corneocyte size, maturity, skin protease activity, protein content and transepidermal water loss. *Br J Dermatol* 2011; 164:1304–10.http://www.ncbi.nlm.nih.gov/pubmed/21443526

Aqueous cream and emollients: Danby S, Cork MJ. A new understanding of atopic dermatitis: the role of epidermal barrier dysfunction and subclinical inflammation. *J ClinDermatol* 2010; 1:33–46.

Aqueous cream and emollients: Hoare C, Li Wan Po A,Williams H. Systematic review of treatments of atopic eczema. Health Technol Assess 2000;4(37).http://www.ncbi.nlm.nih.gov/pubmed/11134919

Aqueous cream and emollients: Lewis-Jones S, Cork MJ, Clark C et al. Atopic Eczema in Children – Guideline Consultation: A Systematic Review of the Treatments for Atopic Eczema and Guideline for its Management. London: National Institute for Clinical Excellence (NICE), 2007.https://www.nice.org.uk/guidance/cg57

[viii] Potent and very potent corticosteroids, topical: Green C, Colquitt JL, Kirby J, Davidson P, Payne E. Clinical and cost-effectiveness of once daily versus more frequent use of same potency topical corticosteroids for atopic eczema: a systematic review and economic evaluation. Health Technol Assess. 2004 Nov;8(47):iii,iv, 1-120. https://www.ncbi.nlm.nih.gov/pubmed/15527669

[ix]Aciclovir, oral: Workowski KA, Bolan GA: Centers for Disease Control and Prevention (CDC). Sexually transmitted diseases treatment guidelines, 2015.MMWR Recomm Rep. 2015;64; RR-3):1-140. http://www.cdc.gov/std/tg2015/tg-2015-print.pdf

[x] Aciclovir, IV: Cernik C, Gallina K, Brodell RT. The treatment of herpes simplex infections:an evidence-based review. Arch Intern Med. 2008 Jun 9;168(11):1137-44.http://www.ncbi.nlm.nih.gov/pubmed/18541820

Aciclovir, IV: South African Medicines Formulary, 14th Edition. Division of Clinical Pharmacology. University of Cape Town, 2022.

[xi] Dressing: Palfreyman SJ, Nelson EA, Lochiel R, Michaels JA. Dressings for healing venous leg ulcers. Cochrane Database Syst Rev. 2006 Jul 19;(3):CD001103. Review.Update in: Cochrane Database Syst Rev. 2014;5:CD001103. http://www.ncbi.nlm.nih.gov/pubmed/16855958

[xii] Potent topical corticosteroids (therapeutic class): South African Medicines Formulary, 14th Edition. Division of Clinical Pharmacology. University of Cape Town, 2022.

[xiii] Potent topical corticosteroids (therapeutic class): South African Medicines Formulary, 14th Edition. Division of Clinical Pharmacology. University of Cape Town, 2022.

[xiv] Potent topical corticosteroids (therapeutic class): South African Medicines Formulary, 14th Edition. Division of Clinical Pharmacology. University of Cape Town, 2022.

[xv] Fluconazole, oral:Gupta AK, Ryder JE, Johnson AM. Cumulative meta-analysis of systemic antifungal agents for the treatment of onychomycosis.Br J Dermatol. 2004 Mar;150(3):537-44. http://www.ncbi.nlm.nih.gov/pubmed/15030339
Fluconazole:Nozickova M, Koudelkova V, Kulikova Z, Malina L, Urbanowski S, Silny W. A comparison of the efficacy of oral fluconazole, 150 mg/week versus 50 mg/day, in the treatment of tinea corporis, tinea cruris, tinea pedis, and cutaneous candidosis.Int J Dermatol. 1998 Sep;37(9):703-5.http://www.ncbi.nlm.nih.gov/pubmed/9762826
Fluconazole: Faergemann J, Mörk NJ, Haglund A, Odegård T. A multicentre (double-blind)
comparative study to assess the safety and efficacy of fluconazole andgriseofulvin in the treatment of tinea corporis and tinea cruris. Br J Dermatol.1997 Apr;136(4):575-7.http://www.ncbi.nlm.nih.gov/pubmed/91559

[xvi] Podophyllotoxin 0.5%, topical: National Department of Health: Affordable Medicines, EDP-Adult Hospital level. Medicine Review: Ano-genital warts, May 2018. https://www.knowledgehub.org.za/content/standard-treatment-guidelines-and-essential-medicines-list.

Podophyllotoxin 0.5%, topical: Thurgar E, Barton S, Karner C, Edwards SJ. Clinical effectiveness and cost-effectiveness of interventions for the treatment of anogenital warts: systematic review and economic evaluation. Health Technol Assess. 2016 Mar;20(24):v-vi, 1-486. https://www.ncbi.nlm.nih.gov/pubmed/27034016

Podophyllin 20% in compound tincture benzoin BP, topical: Thurgar E, Barton S, Karner C, Edwards SJ. Clinical effectiveness and cost-effectiveness of interventions for the treatment of anogenital warts: systematic review and economic evaluation. Health Technol Assess. 2016 Mar;20(24):v-vi, 1-486. https://www.ncbi.nlm.nih.gov/pubmed/27034016

CHAPTER 5
GYNAECOLOGY

5.1 DYSMENORRHOEA
N94.4-6

DESCRIPTION
Lower abdominal pain that starts with the onset of menstruation and subsides after menses have ended. This may be associated with headaches, nausea, and vomiting. It may be primary or secondary. Primary dysmenorrhoea is menstrual pain without organic disease. Secondary dysmenorrhoea is associated with identifiable disease, e.g. chronic pelvic infection, fibroids, endometriosis, adenomyosis; or the use of an intrauterine contraceptive device.

GENERAL MEASURES
For secondary dysmenorrhoea, investigate and treat the underlying condition.

MEDICINE TREATMENT
Symptomatic relief:
- NSAID, e.g.:
- Ibuprofen, oral, 400 mg 8 hourly, with or after a meal.

OR *LoE:IIIb[j]*

- Paracetamol, oral, 500 mg to 1 g, 4 to 6 hourly as required (to a maximum of 4 g in 24 hours).
  - Maximum dose: 15 mg/kg/dose.

LoE:IVb[ji]

LoE:IVb

For dysmenorrhoea caused by endometriosis:

ADD
- Combined oral contraceptive and review after 3 months.

OR *LoE:IIIb[jii]*

- Medroxyprogesterone acetate (long acting), IM, 150 mg 12 weekly.
  - Review after 3 months. *LoE:IIb[jv]*

REFERRAL
» If there is uncertainty about the diagnosis.
» Young women with pain not responding to conventional treatment.
» Older (>40 years of age) women with persistent pain.

5.2 UTERINE BLEEDING, ABNORMAL (AUB)

N92.0–6

DEFINITION

Abnormal uterine bleeding (AUB) is defined as any symptomatic variation from normal menstruation in terms of regularity, frequency, volume, or duration. AUB can either be acute, i.e. an episode of heavy bleeding of a sufficient volume to require immediate intervention to prevent further blood loss, or chronic, i.e. present for more than 6 months.

LoE:IIb[v]

GENERAL MEASURES

» All women >45 years of age with AUB should have a transvaginal ultrasound and endometrial sampling to exclude pathology.
» Actively exclude organic causes, e.g. fibroids, for abnormal uterine bleeding.
» All women should receive a speculum examination to rule out cervical pathology. A cervical cytology smear should be performed if the cervix appears abnormal or if indicated according to the national screening program.

MEDICINE TREATMENT

The management of AUB due to a pathological condition is aimed at that particular pathology. If no organic cause is found, manage medically as follows:

Arrest of acute haemorrhage

- Progestin, e.g.:
- Norethisterone, oral, 5 mg 4 hourly until bleeding stops. *LoE:IVb*[vi]
  - Maximum duration of use: 48 hours.

OR

- Tranexamic acid, oral, 1 g 6 hourly on days 1–4 of the cycle. *LoE:IIa*[vii]

<u>After bleeding has stopped, continue with:</u>

- Combined oral contraceptive, oral, 1 tablet 8 hourly for 7 days.
  - Follow with 1 tablet once daily for 3 months.

For restoring cyclicity (N92.6)

<u>For women in the reproductive years:</u>

- Combined oral contraceptive, oral, 1 tablet daily for 6 months.

OR

<u>Alternative to combined oral contraceptives:</u>

Progestin only:

- Medroxyprogesterone acetate, oral, 30 mg daily from day 5 to day 26 of the cycle. *LoE:IIIb*[viii]
  - Use for 3–6 cycles.

OR

- Norethisterone, oral, 15 mg 8 hourly from day 5 to day 26 of the cycle.
  - Use for 3–6 cycles.

LoE:IIIb[ix]

OR

- NSAID, oral: e.g.
- Ibuprofen, oral, 400 mg 8 hourly with or after a meal for 2 to 3 weeks. *LoE:IIIb*[x]
  - Begin trial of NSAID starting on 1st day of menses until menses cease.

OR

- Tranexamic acid, oral, 1 g 6 hourly on days 1–4 of the cycle.

LoE:IIa[xi]

For perimenopausal women, hormone therapy (HT): N92.4

- Conjugated estrogens, oral, 0.625 mg daily for 21 days.

AND

- Medroxyprogesterone acetate, oral 10 mg daily from day 11 to day 21.
  - Omit treatment from day 22– 28 no treatment.
  - Continue both treatments for 3–6 cycles.

For dysmenorrhoea and abnormal bleeding:

- NSAID, oral, e.g.:
- Ibuprofen, oral, 400 mg 8 hourly for 2–3 days with or after a meal, depending on severity of pain.

REFERRAL

Treatment failure - refer for consideration of levonorgestrel intrauterine system or surgical procedures as dictated by the diagnosis.

5.3 PELVIC INFLAMMATORY DISEASE (PID)

N70.0-1/N70.9/N71.0-1/N71.9/N72/N73.0-6/N73.8-9

DESCRIPTION

Pelvic inflammatory disease (PID) includes salpingitis with or without oophoritis. As precise clinical localisation is often difficult, PID denotes a spectrum of conditions resulting from infection of the upper genital tract.

Sequelae include:

» recurrent infections if inadequately treated,
» infertility,
» increased probability of ectopic pregnancy, and
» chronic pelvic pain.

Stage	Manifestations
Stage I	» cervical motion tenderness and/or uterine tenderness and/or adnexal tenderness
Stage II	» as stage I, plus pelvic peritonitis
Stage III	» as stage II, plus » tubo-ovarian complex or abscess
Stage IV	» generalised peritonitis » ruptured tubo-ovarian complex » septicaemia

GENERAL MEASURES

» Hospitalise all patients with stage II–IV PID for parenteral antibiotic therapy.
» Frequent monitoring of general abdominal and pelvic signs is essential.
» Admission for parenteral therapy, observation, further investigation and/or possible surgical intervention should also be considered in the following situations:
  – a surgical emergency cannot be excluded
  – lack of response to oral therapy
  – clinically severe disease
  – presence of a tubo-ovarian abscess
  – intolerance to oral therapy
  – pregnancy
» In stage III, surgery is indicated if:
  – the diagnosis is uncertain,
  – there is no adequate response after 48 hours of appropriate therapy,
  – the patient deteriorates on treatment, or
  – there is a large or symptomatic pelvic mass after 6 weeks.

Further Investigation

All sexually active patients should be offered:
» a pregnancy test: an ectopic pregnancy forms part of the differential diagnosis.
» screening for sexually transmitted infections including HIV.

Note: Remove IUCD if present and provide alternative contraception.

MEDICINE TREATMENT

Stage I

- Azithromycin, oral, 1 g as a single dose. W

AND *LoE:IIb*[xii]

- Ceftriaxone, IM, 250 mg as a single dose. W
  - Dissolve ceftriaxone, IM, 250 mg in 0.9 mL lidocaine 1% without adrenaline (epinephrine).

AND *LoE:IVb*[xiii]

- Metronidazole, oral, 400 mg 12 hourly for 7 days. A

LoE:IIIb[xiv]

Severe penicillin allergy: (Z88.0)

- Azithromycin, oral, 2 g as a single dose. W

AND

LoE:Ib[xv]

- Metronidazole, oral, 400 mg 12 hourly for 7 days. A

Stage II–IV

- Ceftriaxone, IV, 1 g daily. W

AND

- Metronidazole, IV, 500 mg 8 hourly. A

AND

- Azithromycin, oral, 1 g, as a single dose. W

Continue intravenous therapy until there is definite clinical improvement (within 24-48 hours). Thereafter, change IV therapy to:

- Amoxicillin/clavulanic acid, oral, 875/125 mg 12 hourly to complete 10 days of antibiotic therapy. A

LoE:IIIb[xvi]

Note: The addition of metronidazole to amoxicillin/clavulanic acid is unnecessary as amoxicillin/clavulanic acid has adequate anaerobic cover.

Severe penicillin allergy: (Z88.0)

- Clindamycin, IV, 600 mg 8 hourly. A

AND

- Gentamicin, IV, 6 mg/kg daily. A (see Appendix II for guidance on prescribing.)

AND

- Azithromycin, oral, 1 g, as a single dose. W

LoE:IIIb[xvii]

Continue intravenous therapy until there is definite clinical improvement (within 24-48 hours). Thereafter, change to:

- Clindamycin, oral, 450 mg 8 hourly. A

AND

- Ciprofloxacin, oral, 500 mg 12 hourly to complete 10 days of antibiotic therapy. W

Note: The addition of metronidazole to clindamycin is unnecessary as clindamycin has adequate anaerobic cover.

REFERRAL

» Stages III and IV should be managed in consultation with a gynaecologist.
» For surgical intervention – see indications above.

5.4 ENDOMETRIOSIS

N80.0-6/N80.8-9

DESCRIPTION

The presence and proliferation of endometrial tissue outside the uterine cavity, usually within the pelvis. It may manifest as dysmenorrhoea, dyspareunia, and chronic pelvic pain. Diagnosis is made by laparoscopy.

MEDICINE TREATMENT

For pain:

- NSAID, oral: e.g.
- Ibuprofen, oral, 400 mg 8 hourly with or after a meal. *LoE:IVb*

AND

- Combined oral contraceptives for 6 months.
  OR
- Medroxyprogesterone acetate, oral, 30 mg daily for at least 3 months.

Note: The recurrence of symptoms is common following cessation of treatment.

REFERRAL

» Women with infertility.
» No response to treatment after 3 months.

5.5 AMENORRHOEA

N91.0-2

DESCRIPTION

» Primary amenorrhoea: no menstruation by 16 years of age in the presence of secondary sexual characteristics.
» Secondary amenorrhoea: amenorrhoea for at least 3 months in women with previous regular menses, or for at least 6 months in women with irregular cycles.

Investigations

» Body mass index.
» Urine pregnancy test.
» Pelvic ultrasound.
» Serum for TSH, FSH, LH, prolactin.
  – FSH>15 units/L in a woman <40 years of age suggests premature ovarian failure.
  – LH/FSH ratio of >2:1 suggests polycystic ovarian syndrome.

MEDICINE TREATMENT

For treatment of hyperprolactinaemia, hypo- or hyperthyroidism, see Chapter 8: Endocrine System.

Progestin challenge test:

If no cause for secondary amenorrhoea is found:

- Medroxyprogesterone acetate, oral, 10 mg daily for 10 days.
  - Anticipate a withdrawal bleed 5–7 days following conclusion of treatment.

REFERRAL

» All cases of primary amenorrhoea.
» Secondary amenorrhoea not responding to medroxyprogesterone acetate.
» Polycystic ovarian syndrome and premature ovarian failure, for further evaluation.

5.6 HIRSUTISM AND VIRILISATION

L68.0/E25.0/E25.9

DESCRIPTION

Hirsutism refers to terminal hair growth in amounts that are socially undesirable, typically following a male pattern of distribution. Virilisation refers to the development of male secondary sexual characteristics in a woman.

REFERRAL

Refer all cases to a tertiary hospital for investigation and management.

5.7 INFERTILITY

N97.0-4/N97.8-9

DESCRIPTION

Inability to conceive after a year of regular sexual intercourse without contraception.

GENERAL MEASURES

» Counselling.
» Lifestyle modification, e.g. weight optimisation, smoking cessation, and regular sexual intercourse.

Investigations

» Partner semen analysis.
» Anti-mullerian hormone (AMH) levels to evaluate ovarian reserve (>1.1 ng/ml suggests good ovarian reserve).
» If AMH is unavailable - Mid-luteal (day 21) progesterone assay: >30 nmol/L suggests adequate ovulation (Specialist indication).
» Laparoscopy and/or hysterosalpingography. (Specialist supervision.)

MEDICINE TREATMENT

Treat the underlying disease.

For induction of ovulation in women with confirmed anovulation:

» **There are two options available: letrozole or clomifene.**
» Letrozole is likely to result in more pregnancies and sooner pregnancies but both agents are effective.
» Administer letrozole following a spontaneous menses or a medroxyprogesterone acetate withdrawal bleed.

- Letrozole 2.5 mg daily on days 3-7 of the cycle. (Specialist only.)

LoE:IIb[xviii]

Note:

» Letrozole for ovulation induction is an off-label indication. Counsel patient and obtain patient consent.
» Consider the use of an alternative agent in patients with moderate or severe hepatic disease, porphyria, or osteoporosis.

If letrozole cannot be used:

- Clomifene, oral, 50 mg daily on days 5–9 of the cycle. (Specialist only.)
  - Monitor the progress of ovulation.

LoE:IIb[xix]

For hyperprolactinaemia after further investigation:
See Section 8.15.1: Prolactinoma.

Note: Women should be counselled on the risk of multiple births with ovulation inducing medicines.

5.8 MISCARRIAGE

Both manual vacuum aspiration (MVA) and medical evacuation are equally effective for miscarriage. However, MVA is preferred in the follow settings:

» anaemia,
» haemodynamic instability,
» second trimester miscarriage.

5.8.1 SILENT MISCARRIAGE OR EARLY FETAL DEATH

O02.1

GENERAL MEASURES

» Counselling.
» Evacuation of the uterus.

MEDICINE TREATMENT

Before MVA, to ripen the cervix:

- Misoprostol, PV, 400 mcg as a single dose.

Medical evacuation: (O04.9)

- Misoprostol, oral/PV, 600 mcg as a single dose.
  - Repeat after 24 hours if necessary.

5.8.2 INCOMPLETE MISCARRIAGE IN THE FIRST TRIMESTER

O03.3-4

GENERAL MEASURES

» Counselling.
» Evacuation of the uterus.

MEDICINE TREATMENT

Before MVA, to ripen the cervix (if needed):

- Misoprostol, oral/PV, 400 mcg as a single dose.

Medical evacuation: (O04.9)

- Misoprostol, SL/PV/buccal, 800 mcg immediately as a single dose.
  - Repeat after 24 hours if necessary. *LoE:IIIb*[xx]

Routine analgesia for vacuum aspiration:

- Morphine, IM, 0.1 mg/kg 30 minutes before aspiration procedure, to a maximum of 10 mg. (Doctor prescribed.) *LoE:IVb*[xxi]

Alternatively, consider paracervical block - see Section 5.9.1: TOP: Management of pregnancies up to the twelfth week of gestation (12 weeks and 0 days).

Oral analgesia as required for 48 hours:

- Paracetamol, oral, 500 mg to 1 g, 4 to 6 hourly as required (to a maximum of 4 g in 24 hours).
  - Maximum dose: 15 mg/kg/dose.

AND

- Ibuprofen, oral, 400 mg 8 hourly with or after a meal, if needed.

Note:

» Follow up after one week to ensure that bleeding has stopped, or sooner with worsening symptoms.
» Perform a pregnancy test three weeks after medical management. *LoE:IIIb*[xxii]

5.8.3 MIDTRIMESTER MISCARRIAGE (FROM 13–22 WEEKS GESTATION)

O03.3-4/O03.9

GENERAL MEASURES

» Counselling.
» Evacuation of the uterus after the fetus has been expelled.

MEDICINE TREATMENT

If cervical dilatation needed:

- Misoprostol, PV/SL/buccal, 200 mcg every 4–6 hours until products of conception have been expelled.
  - Duration of treatment must not exceed 5 doses within 24 hours.

LoE:IIIb[xxiii]

Previous Caesarean delivery:

- Misoprostol, PV/SL/buccal 100 mcg every 4–6 hours products of conception have been expelled.
  - Duration of treatment must not exceed 5 doses within 24 hours.

LoE:IIIb[xxiv]

If cervical dilatation already present:

- Oxytocin, IV.
  - Dilute 20 units in 1 L sodium chloride 0.9%, i.e. 20 milliunits/mL solution, and infuse at 125 mL/hour.
  - Reduce rate if strong contractions are experienced.

  Note: Check serum sodium if used for more than 24 hours because of the danger of dilutional hyponatraemia.

For analgesia:

- Morphine, IV, to a maximum dose of 10 mg. (See Appendix II, for individual dosing and monitoring for response and toxicity.)

If Rh-negative: (O36.0)

- Anti-D immunoglobulin, IM, 100 mcg as a single dose.

REFERRAL

» Uterine abnormalities.
» Recurrent miscarriages (3 consecutive spontaneous miscarriages).
» Suspected cervical weakness: mid-trimester miscarriage(s) with minimal pain and bleeding.
» Diabetes mellitus.
» Parental genetic defects and SLE or other causes of autoimmune disease.

5.8.4 SEPTIC MISCARRIAGE

O03.0/O03.5 + (A41.9/N71.0/R57.2)

GENERAL MEASURES

» Counselling.

» Urgent evacuation of uterus (under general anaesthesia and not an MVA) and surgical management of complications.

MEDICINE TREATMENT

- Oxytocin, IV.
  - Dilute 20 units in 1 L sodium chloride 0.9%, i.e. 20 milliunits/mL solution administered at a rate of 125 mL/hour.
  - Reduce infusion rate if strong contractions are experienced.

Antibiotic therapy

- Amoxicillin/clavulanic acid, IV, 1.2 g, 8 hourly. A

Change to oral treatment after clinical improvement:

- Amoxicillin/clavulanic acid, oral, 875/125 mg 12 hourly for 7–10 days. A

Note: The addition of metronidazole to amoxicillin/clavulanic acid is unnecessary as amoxicillin/clavulanic acid has adequate anaerobic cover.

LoE:IVb

Severe penicillin allergy: (Z88.0)

- Clindamycin, IV, 600 mg 8 hourly. A

AND

- Gentamicin, IV, 6 mg/kg daily. A (See Appendix II for guidance on prescribing.)

Change to oral treatment after improvement:

- Clindamycin, oral, 450 mg 8 hourly for 5 days. A

AND

- Ciprofloxacin, oral, 500 mg 12 hourly for 5 days. W

Note: The addition of metronidazole to clindamycin is unnecessary as clindamycin has adequate anaerobic cover.

If patient has severe sepsis, consider urgent hysterectomy.

REFERRAL

» Evidence of trauma.
» No response to treatment within 48 hours.

5.8.5 TROPHOBLASTIC NEOPLASIA ('HYDATIDIFORM MOLE')

O01.0-1/O01.9

GENERAL MEASURES

» Misoprostol is not indicated in this condition because of risk of dissemination.
» Send products of conception for histology.

REFERRAL

All patients.

5.9 TERMINATION OF PREGNANCY (TOP)

Early ultrasound examination is more accurate than last normal menstrual period at determining gestational age and is also useful in identifying ectopic-, molar-, or twin pregnancies.

The clinical management for all pregnancies up to 14 weeks can be done as outpatient procedures. From 14 weeks onwards, TOP should be done in a medical facility. Note that the gestational ages used for clinical management differ from the legal cut-offs, e.g. a patient at 12 weeks and 1 day will meet the legal requirements as described in the act for TOP after 12 weeks, but the clinical management is the same as for a pregnancy from day one up to 14 weeks (see below). The legal criteria for TOP follow below.

Summary of Choice of Termination of Pregnancy Act of 1996
Women eligibility

Up to 12 completed weeks and 0 days: On request.

From the thirteenth week (12 weeks and 1 day) up to the twentieth week (20 weeks and 0 days): "If the doctor is of the opinion that: i) the pregnancy resulted from rape or incest, ii) there is substantial risk of severe fetal physical or mental abnormality, iii) the continued pregnancy poses a risk to mother's physical or mental health, or social/economic circumstances".

More than 20 weeks (≥ 20 weeks 1 day): "If the doctor, after consulting with a second doctor or registered midwife, is of the opinion that continued pregnancy: i) would endanger the mother's life, or ii) would result in risk of injury or severe malformation to the fetus"

Venue

An accredited facility with staff trained in performing TOP, designated by the Member of Executive Council at provincial level. A facility with a 24-hour maternity service does not require specific designation - *The Choice on Termination of Pregnancy Act, 1996 (as amended by Act 38 of 2004), expands access to TOP services, allowing registered nurses, as well as registered midwives, to perform TOPs up to the twelfth week of pregnancy.*

Practitioner

Up to 12 weeks and 0 days: Doctor, midwife, or registered nurse with appropriate training.

From the thirteenth week (12 weeks and 1 day) up to the twentieth week (20 weeks and 0 days): Doctor responsible for decision and prescription of medication; registered nurse/midwife may administer medication according to prescription.

Note:

» Pre-and post-termination counselling and contraceptive counselling is essential.
» Consent of spouse/partner is not necessary.

» Consent for TOP and related procedures e.g. laparotomy may be given by minors. Minors are encouraged to consult parents or others, but consent is not mandatory.

5.9.1 TOP: MANAGEMENT OF PREGNANCIES UP TO THE TWELFTH WEEK OF GESTATION (12 WEEKS AND 0 DAYS)

O04.9/O06.9

GENERAL MEASURES

» Counselling.
» Outpatient procedure by nursing staff with specific training.
» Discuss TOP options with patient: Medical TOP or manual vacuum aspiration of the uterus.

LoE:IIIb[xxv]

MEDICINE TREATMENT

Medical TOP:

(Up to 12 weeks and 0 days)

- Mifepristone, oral, 200 mg, immediately as a single dose. *LoE:IIb*[xxvi]

Followed 1-2 days later by:

- Misoprostol, PV/SL/buccal, 800 mcg by self-administration
  - If expulsion has not occurred 4 hours after misoprostol administration, a second dose of misoprostol 400 mcg may be given.

Note: Bleeding may persist for up to 1 week. If there is no bleeding after the second dose of misoprostol, the woman must return to the facility as soon as possible as there is a possibility of an incomplete procedure or ectopic pregnancy.

LoE:IIIb[xxvii]

For pain:

- Paracetamol, oral, 500 mg to 1 g, 4 to 6 hourly as required (to a maximum of 4 g in 24 hours).
  - Maximum dose: 15 mg/kg/dose.

ADD

After expulsion is complete:

- NSAID, e.g.:
- Ibuprofen, oral, 400 mg 8 hourly with or after a meal.

Manual vacuum aspiration:

- Misoprostol, PV, 400 mcg 3 hours before routine vacuum aspiration of the uterus.

Routine analgesia for vacuum aspiration:

- Morphine, IM, 0.1 mg/kg 30 minutes before aspiration procedure, to a maximum of 10 mg. *LoE:IVb*[xxviii]

Do not give intravenous benzodiazepines and parenteral opioid analgesics concurrently.

Alternatively, consider a paracervical block:

- Use lidocaine 1% (without adrenaline).
  - Draw up lidocaine 1% in a 20 mL syringe.
  - Attach a 20-gauge spinal needle. Inject 2 mL superficially in the cervix at 12h00 and immediately grab the cervix with a tenaculum at 12h00 to stabilise cervix.
  - Inject remaining 18 mL slowly over 60 seconds into the cervicovaginal junction in four equal doses of 4–5mL at 2, 4, 8, and 10 o'clock (see Figure 5.1: Anterior view of the cervix).
  - This injection is continuous from superficial to deep (a depth of 3 cm) and again to superficial (injecting with insertion and withdrawal).
  - Manual vacuum aspiration can start after 3 minutes.

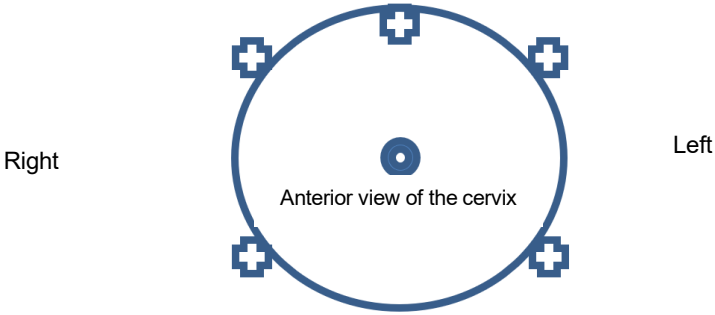


Figure 5.1: Anterior view of the cervix

LoE:IIIb[xxix]

Oral analgesia as required for 48 hours:

- Paracetamol, oral, 500 mg to 1 g, 4 to 6 hourly as required (to a maximum of 4 g in 24 hours).
  - Maximum dose: 15 mg/kg/dose.

AND

- NSAID, e.g.:
- Ibuprofen, oral, 400 mg 8 hourly with or after a meal.

5.9.2 TOP: FROM THE THIRTEENTH WEEK (12 WEEKS AND 1 DAY) UP TO THE TWENTIETH WEEK (20 WEEKS AND 0 DAYS)

O04.9/O06.9

GENERAL MEASURES

» Medical TOP: From 12 weeks onwards, this should be performed as an in-patient with 24-hour services and facilities for general anaesthesia, as there is a greater risk for bleeding or a need for surgical completion of the procedure.

LoE:IIIb[xxx]

» Manual vacuum aspiration can be performed up to 14 weeks. Dilation and sharp curettage (D&C) are not recommended and should preferably be replaced by vacuum aspiration.

LoE:IVb[xxxi]

» Surgical TOP (dilatation and evacuation procedure after cervical preparation) can be done by specially trained providers as a day theatre procedure after 14 weeks.

MEDICINE TREATMENT

Medical TOP:

- Mifepristone, oral, 200 mg, oral, immediately as a single dose.

LoE:IIb[xxxii]

Follow 1-2 days later with:

- Misoprostol, PV/SL/buccal, 400 mcg, every 3 hours until TOP occurs.

LoEIIIb[xxxiii]

LoE:IIIb[xxxiv]

Analgesia:

- Morphine, IM, 0.1 mg/kg 4 hourly or as needed, to a maximum of 10 mg.

If Rh-negative: O36.0

- Anti-D immunoglobulin, IM, 100 mcg as a single dose.

Contraception:

Counsel all women on effective contraception, especially long-acting reversible methods. All methods can be given at the time of the procedure, except for an IUCD after a medical TOP. IUCD may be inserted after medical TOP if reasonably certain that individual is no longer pregnant.

Note:

Medical TOP should be followed by manual vacuum aspiration of the uterus if expulsion of products of conception is not complete.

Cervical preparation for manual vacuum aspiration or surgical TOP:

- Misoprostol PV/SL, 400 mcg, 2 to 3 hours prior to the procedure.

REFERRAL
» Complicating medical conditions, e.g. cardiac failure, etc.
» Failed procedure.
» Ectopic pregnancy.

5.10 SEXUAL ASSAULT
T74.2 + (Y05.0-99)

INVESTIGATIONS
» Urine pregnancy test.
» Blood for:
  – Syphilis serology.
  – HIV.
  – Hepatitis B if no history of previous Hep B immunisation.

GENERAL MEASURES
» Trauma counselling and completion of J88 forms.
» Examination under anaesthesia may be required for adequate forensic sample collection, or repair of genital tract trauma.

MEDICINE TREATMENT
Emergency contraception (Z29.8)
» Do a pregnancy test in all women and female adolescents.
» Children must be tested and provided with emergency contraception from Breast Tanner Stage III.
» If unsure of staging, give emergency contraception in the presence of any breast development (DO NOT REGARD MENARCHE AS AN INDICATION).
▪ Copper IUCD, e.g.:
• Cu T380A, inserted as soon as possible after unprotected intercourse and not later than 5 days.

LoE:IIIb[xxxv]

OR
• Levonorgestrel 1.5 mg, oral, as a single dose as soon as possible after unprotected intercourse, and not later than 5 days.
  ○ If the person vomits within 2 hours, repeat the dose.

LoE:Ia[xxxvi]

Note:
» Advise women that the emergency contraception should not affect their usual menstrual cycle: very rarely it is delayed but it should not be more than 7 days late. If this occurs, they should come back for a pregnancy test.

CAUTION

» Emergency contraceptive tablets must be taken as soon as possible, preferably within 72 hours of unprotected intercourse, and not later than 5 days.
» Enzyme inducers (including efavirenz, carbamazepine, and rifampicin) cause a significant reduction in levonorgestrel concentrations. Women on these medicines should preferably have copper IUCD inserted or alternatively double the dose of levonorgestrel.
» Women weighing > 80 kg or with a BMI ≥ 30 should also preferably have copper IUCD inserted, or alternatively, double the dose of levonorgestrel. *LoE:IIIb[xxxvii]*

If there is vomiting (Z29.8):

- Metoclopramide oral, 10 mg 8 hourly or as needed.

LoE:IVb

STI prophylaxis (Z29.8):

- Ceftriaxone, IM, 250 mg as a single dose. W
  - For ceftriaxone IM injection: Dissolve ceftriaxone 250 mg in 0.9 mL lidocaine 1% without adrenaline (epinephrine).

AND

- Azithromycin, oral, 1 g, as a single dose. W

LoE:IIIb[xxxviii]

AND

- Metronidazole, oral, 2 g immediately as a single dose. A

HIV post-exposure prophylaxis (PEP) (Z20.6+Z29.8):
See Section 10.5.3: Non-occupational post exposure prophylaxis, inadvertent non-occupational.

5.11 URINARY INCONTINENCE

DESCRIPTION

» The involuntary leak of urine. Occurs in 10-17% of all women.
» Risk factors include age (prevalence and severity increase with age), increased parity, obesity, smoking, caffeine intake, diabetes and menopausal vaginal atrophy.
» Most common types are stress incontinence, urgency incontinence (overactive bladder) or a mixed incontinence (features of both stress and urgency).

5.11.1 STRESS INCONTINENCE

N39.3

DESCRIPTION

» Incontinence that occurs with increased abdominal pressure (e.g. cough, sneeze or laugh) in the absence of a bladder contraction.

GENERAL MEASURES
» Exclude urinary tract infection or diabetes.
» Pelvic examination to exclude pelvic masses, pelvic organ prolapse, or menopausal vaginal atrophy.
» Stop smoking.
» Manage obesity.
» Reduce or avoid caffeine.
» Reduce alcohol intake.
» Manage constipation and avoid excessive fluid intake.
» Keep a bladder diary.
» Pelvic floor exercises (see Section 7.3.6: Overactive bladder).

MEDICINE TREATMENT
There is insufficient evidence for the use of pharmacological interventions to treat stress incontinence.

REFERRAL
» If any pelvic pathology, immediate referral to specialist.
» If no underlying pathology, refer for bladder stress testing if no improvement with conservative measures after 3-6 months.

5.11.2 URGENCY INCONTINENCE (OVERACTIVE BLADDER)
See Section: 7.3.6: Overactive bladder.

5.12 MENOPAUSE AND PERIMENOPAUSAL SYNDROME
N95.0-3/N95.8-9

For primary management with hormone therapy (HT), refer to the PHC STGs and EML, Section 6.13: Hormone therapy (HT).

If HT is contra-indicated, poorly tolerated or ineffective:
- Fluoxetine, oral. *LoE:IIIb[xxxix]*
  - Initiate at 20 mg on alternate days.
  - If there is no response after 12 weeks, increase the dose to 20 mg daily.

<u>If on tamoxifen:</u> *LoE:IIIb[xl]*
- Citalopram, oral, 10 mg daily.
  - If there is no response after 12 weeks, increase the dose to 20 mg daily.

Note:
Start at the lowest possible dose to alleviate symptoms. The need to continue therapy should be reviewed annually.

REFERRAL

» Premature menopause, i.e. <40 years of age.
» Severe osteoporosis.
» Post-menopausal bleeding.
» Hormone-dependent cancers, thrombo-embolism, liver disease; and unacceptable side-effects to hormone replacement therapy e.g. exacerbation of depression, enlargement of uterine fibroids, exacerbation of endometrioses (see Section 5.4: Endometriosis).

5.13 MEDICAL MANAGEMENT OF ECTOPIC PREGNANCY

O00.0-2/O00.8-9

GENERAL MEASURES

» Ruptured or suspected rupture of an ectopic pregnancy should be managed with urgent resuscitation and surgery.
» There must be certainty that there is no viable intra-uterine pregnancy.
» The discriminatory zone is the β-hCG level above which an ultrasound is likely to visualise a gestational sac within the uterus in a normal intra-uterine pregnancy (>1500 IU/L for a transvaginal ultrasound).
» If the initial β-hCG level is below the discriminatory threshold (or level) to diagnose a pregnancy on transvaginal ultrasound, or the ultrasound cannot definitively identify an intrauterine or extra-uterine gestation, then serial β-hCG measurements are necessary to differentiate between a growing, potentially viable pregnancy, and a non-viable pregnancy.
» A minimum rise in β-hCG of 53% every two days is expected for a potentially viable pregnancy in women who present with symptoms of pain and/or vaginal bleeding.
» Repeat the β-hCG in 48 hours:
  – If the level has dropped, conservative management may be appropriate.
  – If the level has increased by >50% or is now above the discriminatory zone, repeat the ultrasound scan to exclude an intra-uterine pregnancy before methotrexate is administered.

LoE:IIIb[xli]

MEDICINE TREATMENT

Methotrexate should be the first-line management for women who are able to return for follow-up and who have the following characteristics:
» haemodynamic stability and no significant pain.
» an unruptured ectopic pregnancy with a mass <35 mm and no visible heartbeat.
» low serum β-hCG, ideally less than 1500 IU/L but can be up to 5000 IU/L.
» certainty that there is no intrauterine pregnancy.
» willingness to attend for follow-up.

There are single and multiple dose methotrexate protocols available. The single dose protocol is less expensive, requires less intensive monitoring and does not require folinic acid rescue. The single dose protocol is recommended for the medical management of ectopic pregnancy. *LoE:IIb*[xlii]

Methotrexate single-dose protocol:
Day 1: Check urea, creatinine, ALT and FBC to exclude abnormalities.

- Methotrexate, IM, 50 mg/m^2 of body surface area (BSA).
  - BSA may be calculated based upon height (cm) and weight (kg) on the day of treatment using the following formula:

$$BSA\ (m^2) = \sqrt{\frac{(Height\ x\ Weight)}{3600}}$$

Day 4: Repeat β-hCG.
Day 7: Repeat β-hCG.

<u>If the decrease from day 4 to day 7 is ≥15%:</u>
» Continue with weekly β-hCG until undetectable.

<u>If decrease <15% and patient still fulfils the criteria for medical management:</u>

- Methotrexate, IM, 50 mg/m^2 BSA.

LoE:IIb[xliii]

Day 14: Repeat β-hCG.

CAUTION

» Methotrexate is associated with blood disorders and is hepatotoxic.
» Caution patients and their carers to immediately report the onset of any feature of blood disorders (e.g. sore throat, bruising, and mouth ulcers), liver toxicity (e.g. nausea, vomiting, abdominal discomfort and dark urine), and respiratory effects (e.g. shortness of breath).

LoE:IVb[xliv]

REFERRAL

If the decline in β-hCG is still <15% on day 14 after two doses of methotrexate, refer for specialist care.

5.14 FAMILY PLANNING REFERRALS FROM PRIMARY CARE

5.14.1 INTRA-UTERINE CONTRACEPTIVE COPPER OR LEVONORGESTREL DEVICE

GENERAL MEASURES

Where there is excessive bleeding after insertion of IUCD or levonorgestrel device:
N92.0-1 + (Z30.5)
» Exclude perforation of the uterus.

Irregular bleeding and/or cramping for >3 months:
N92.1/N92.5-6/N94.5-6/R25.2 + (Z30.5)
» Exclude cervical or pelvic infection, partial expulsion, intrauterine or ectopic pregnancy (rare) or other pathology.

If no pathology is detected:
» Counsel women that irregular bleeding can take up to 6 months to resolve.

MEDICINE TREATMENT

If no pathology is detected:
- NSAID, e.g.:
- Ibuprofen, oral, 400 mg 8 hourly with or after a meal for 5 days. Use for every cycle for 1–3 months. *LoE:IIb*[xlv]
  - Follow up after three months and if bleeding/cramping is unacceptable, offer alternative contraception and remove intra-uterine device.

5.14.2 IMPLANTS

Failure to locate an implant (in the arm) by palpation:
T85.9 + (Z30.4)
» Ultrasound guided removal of deep implants must be done by specially trained providers at regional hospitals.

5.14.3 INJECTABLE CONTRACEPTION

GENERAL MEASURES

Heavy or prolonged bleeding despite adequate treatment with combined oral contraceptives:

N92.0-1 + (Z30.4/Z30.8-9)

» Do thorough gynaecological examination to exclude other pathology.

» Check haemoglobin and prescribe iron if needed. See Section 2.1.1 Anaemia, iron deficiency.

»

MEDICINE TREATMENT

- Ethinylestradiol, oral, 50 mcg daily for 3 months. *LoE:IVb*

OR

- Combined oral contraceptive, containing 50 mcg ethinylestradiol, oral, for 3 months.

If no response to high dose ethinylestradiol, replace with:

- NSAID, e.g.:
- Ibuprofen, oral, 400 mg 8 hourly with or after a meal for 5 days. *LoE:IVb*[xlvi]

If no response to NSAID, replace with:

- Tranexamic acid, oral, 500 mg 8 hourly for 4 days.

LoE:IIb[xlvii]

If there is no response to above-mentioned treatment:

» Change to another method of contraception. See PHC Standard Treatment Guidelines and Essential Medicines List, Chapter 7: Family planning.

References:

[i] Ibuprofen (ceiling effect): Laska EM, Sunshine A, Marrero I, Olson N, Siegel C, McCormick N. The correlation between blood levels of ibuprofen and clinical analgesic response. ClinPharmacolTher. 1986 Jul;40(1):1-7..http://www.ncbi.nlm.nih.gov/pubmed/3522030

[ii] Paracetamol, oral: South African Medicines Formulary, 14th Edition. Division of Clinical Pharmacology. University of Cape Town, 2022.

[iii] Combined oral contraceptive (dysmenorrhea caused by endometriosis): Wong CL, Farquhar C, Roberts H, Proctor M. Oral contraceptive pill for primary dysmenorrhoea. Cochrane Database Syst Rev. 2009 Oct 7;(4):CD002120. http://www.ncbi.nlm.nih.gov/pubmed/19821293

Combined oral contraceptive (dysmenorrhea caused by endometriosis): American College of Obstetricians and Gynecologists. ACOG practice bulletin no. 110: noncontraceptive uses of hormonal contraceptives. Obstet Gynecol. 2010;115(1):206-218.http://www.ncbi.nlm.nih.gov/pubmed/20027071

Combined oral (dysmenorrhea caused by endometriosis): Davis L, Kennedy SS, Moore J, Prentice A. Modern combined oral contraceptives for pain associated with endometriosis. Cochrane Database Syst Rev. 2007 Jul 18;(3):CD001019. http://www.ncbi.nlm.nih.gov/pubmed/17636650

iv Medroxyprogesterone acetate, IM:SchlaffWD, Carson SA, Luciano A, Ross D, Bergqvist A. Subcutaneous injection of depot medroxyprogesterone acetate compared with leuprolide acetate in the treatment of endometriosis-associated pain. FertilSteril. 2006 Feb;85(2):314-25. http://www.ncbi.nlm.nih.gov/pubmed/16595206

Medroxyprogesterone acetate, IM:Crosignani PG, Luciano A, Ray A, Bergqvist A. Subcutaneous depot medroxyprogesterone acetate versus leuprolide acetate in the treatment of endometriosis-associated pain. Hum Reprod 2006; 21:248–256.http://www.ncbi.nlm.nih.gov/pubmed/16176939

v Abnormal uterine bleeding: Abnormal uterine bleeding - Symptoms, diagnosis and treatment | BMJ Best Practice [Internet]. Bmj.com. 2023 [cited 2024 Jan 3]. Available from: https://bestpractice.bmj.com/topics/en-gb/658#:~:text=Definition,%2Dmenstrual%20bleeding%20(IMB).

[vi] Progestin, oral (therapeutic class – arrest of acute haemmhorhage): James AH, Kouides PA, Abdul-Kadir R, Dietrich JE, Edlund M, Federici AB, Halimeh S, Kamphuisen PW, Lee CA, Martínez-Perez O, McLintock C, Peyvandi F, Philipp C, Wilkinson J, Winikoff R. Evaluation and management of acute menorrhagia in women with and without underlying bleeding disorders: consensus from an international expert panel. Eur J ObstetGynecolReprod Biol. 2011 Oct;158(2):124-34. http://www.ncbi.nlm.nih.gov/pubmed/21632169

[vii] Tranexamic acid: Bryant-Smith AC, Lethaby A, Farquhar C, Hickey M. Antifibrinolytics for heavy menstrual bleeding. Cochrane Database Syst Rev. 2018 Apr 15;4(4):CD000249 https://pubmed.ncbi.nlm.nih.gov/29656433/

Tranexamic acid: Leminen H, Hurskainen R. Tranexamic acid for the treatment of heavy menstrual bleeding: efficacy and safety. Int J Womens Health. 2012;4:413-21. http://www.ncbi.nlm.nih.gov/pubmed/22956886

Tranexamic acid: Sundström A, Seaman H, Kieler H, Alfredsson L. The risk of venous thromboembolism associated with the use of tranexamic acid and other drugs used to treat menorrhagia: a case-control study using the General Practice Research Database. BJOG. 2009 Jan;116(1):91-7. http://www.ncbi.nlm.nih.gov/pubmed/19016686

[viii] Progestin,oral (therapeutic class – restoring cyclicity): Singh S, Best C, Dunn S, Leyland N, Wolfman WL; Clinical Practice – Gynaecology Committee, Leyland N, Wolfman W, Allaire C, Awadalla A, Best C, Dunn S, Heywood M, Lemyre M, Marcoux V, Menard C, Potestio F, Rittenberg D, Singh S; Society of Obstetricians and Gynaecologists of Canada. Abnormal uterine bleeding in pre-menopausal women. J ObstetGynaecol Can. 2013 May;35(5):473-9. http://www.ncbi.nlm.nih.gov/pubmed/23756279

Progestin,oral (therapeutic class – restoring cyclicity):Sweet MG, Schmidt-Dalton TA, Weiss PM, Madsen KP. Evaluation and management of abnormal uterine bleeding in premenopausal women. Am Fam Physician. 2012 Jan 1;85(1):35-43. http://www.ncbi.nlm.nih.gov/pubmed/22230306

[ix] Norethisterone Dose: Irvine GA, Campbell-Brown MB, Lumsden MA, Heikkila A, Walker JJ, Cameron IT. Randomised comparative trial of the levonorgestrel intrauterine system and norethisterone for treatment of idiopathic menorrhagia. Br. J. Obstet. Gynaecol. 1998;105(6):592–598

Norethisterone Dose: Hatem Abu Hashim; Waleed Alsherbini; Mohamed Bazeed (2012). Contraceptive vaginal ring treatment of heavy menstrual bleeding: a randomized controlled trial with norethisterone. , 85(3), 0–252. doi:10.1016/j.contraception.2011.07.012

[x] NSAID: Christelle K, Norhayati MN, Jaafar SH. Interventions to prevent or treat heavy menstrual bleeding or pain associated with intrauterine-device use. Cochrane Database Syst Rev. 2022 Aug 26;8(8):CD006034. https://pubmed.ncbi.nlm.nih.gov/36017945/

[xi] Tranexamic acid, oral: Bryant-Smith AC, Lethaby A, Farquhar C, Hickey M. Antifibrinolytics for heavy menstrual bleeding. Cochrane Database Syst Rev. 2018 Apr 15;4(4):CD000249 https://pubmed.ncbi.nlm.nih.gov/29656433/

Tranexamic acid, oral: Callender ST, Warner GT, Cope E. Treatment of menorrhagia with tranexamic acid. A double-blind trial. Br Med J. 1970 Oct 24;4(5729):214-6. http://www.ncbi.nlm.nih.gov/pubmed/4919554

[xii] Azithromycin: Savaris RF, Teixeira LM, Torres TG, Edelweiss MI, Moncada J, Schachter J. Comparing ceftriaxone plus azithromycin or doxycycline for pelvic inflammatory disease: a randomized controlled trial. ObstetGynecol.2007Jul;110(1):53-60.http://www.ncbi.nlm.nih.gov/pubmed/17601896

Azithromycin (LAP/ SSW/ BUBO): Amsden GW, Gray CL. Serum and WBC pharmacokinetics of 1500 mg of azithromycin when given either as a single dose or over a 3 day period in healthy volunteers. J AntimicrobChemother.2001Jan;47(1):61-6. http://www.ncbi.nlm.nih.gov/pubmed/11152432

Azithromycin (LAP/ SSW/ BUBO): Sampson MR, DumitrescuTP, Brouwer KL, Schmith VD. Population pharmacokinetics of azithromycin in whole blood, peripheral blood mononuclear cells, and polymorphonuclear cells in healthy adults.*CPT*PharmacometricsSystPharmacol.2014 Mar 5;3:e103. http://www.ncbi.nlm.nih.gov/pubmed/24599342

[xiii] Lidocaine 1% without adrenaline (epinephrine): MCC/SAHPRA registered package inserts of Kocef® 250 mg, 500 mg, 1 g; Rociject® 500 mg, 1 g; Oframax® 250 mg, 1 g.

[xiv] Metronidazole, oral Bignell C, Fitzgerald M; Guideline Development Group; British Association for Sexual Health and HIV UK. UK national guideline for the management of gonorrhoea in adults, 2011.Int J STD AIDS. 2011 Oct;22(10):541-7. http://www.ncbi.nlm.nih.gov/pubmed/21998172

Metronidazole, oral: Workowski KA, Berman S; Centers for Disease Control and Prevention (CDC). Sexually transmitted diseases treatment guidelines, 2010.MMWRRecomm Rep. 2010 Dec 17;59(RR-12):1-110. Erratum in: MMWRRecomm Rep. 2011 Jan 14;60(1):18. Dosage error in article text. http://www.cdc.gov/std/treatment/2010/

[xv]Azithromycin, oral, 2 g (Severe penicillin allergy): Azithromycin: Pitsouni E, Iavazzo C, Athanasiou S, Falagas ME. Single-dose azithromycin versus erythromycin or amoxicillin for Chlamydia trachomatis infection during pregnancy: a meta-analysis of randomised controlled trials. Int J AntimicrobAgents.2007Sep;30(3):213-21. http://www.ncbi.nlm.nih.gov/pubmed/17596917

[xvi] Antibiotic therapy for stage II-IV PID: Centers for Disease Control and Prevention. Sexually Transmitted Diseases Treatment Guidelines, 2015. MMWRRecomm Rep 2015;64(No. RR-3): 1-137.

[xvii] Antibiotic therapy for stage II-IV PID (Severe pencillin allergy): Centers for Disease Control and Prevention. Sexually Transmitted Diseases Treatment Guidelines, 2015. MMWRRecomm Rep 2015;64(No. RR-3): 1-137.

[xviii] Letrozole, oral: National Department of Health: Affordable Medicines, EDP-Adult Hospital level. Medicine Review: Letrozole for infertility associated with anovulation, April 2020. https://www.knowledgehub.org.za/content/standard-treatment-guidelines-and-essential-medicines-list

Letrozole, oral: Franik S, Eltrop SM, Kremer JA, Kiesel L, Farquhar C. Aromatase inhibitors (letrozole) for subfertile women with polycystic ovary syndrome. Cochrane Database Syst Rev. 2018;5(5):CD010287. https://pubmed.ncbi.nlm.nih.gov/29797697/

[xix] Clomifene, oral: Franik S, Eltrop SM, Kremer JA, Kiesel L, Farquhar C. Aromatase inhibitors (letrozole) for subfertile women with polycystic ovary syndrome. Cochrane Database Syst Rev. 2018;5(5):CD010287. https://pubmed.ncbi.nlm.nih.gov/29797697/

Clomifene, oral: National Department of Health: Affordable Medicines, EDP-Adult Hospital level. Medicine Review: Letrozole for infertility associated with anovulation, April 2020https://www.knowledgehub.org.za/content/standard-treatment-guidelines-and-essential-medicines-list

[xx] Misoprostol (medical abortion): NICE. Guideline: Abortion Care, 25 September 2019. https://www.nice.org.uk/guidance/ng140

Misoprostol (medical abortion): WHO. Guideline: Medical management of abortion, 2018. https://www.who.int/reproductivehealth/publications/medical-management-abortion/en/

[xxi] Morphine, IM (Incomplete 1st trimester miscarriage): National Department of Health, Essential Drugs Programme: Adult Hospital Level STGs and EML, updated edition. https://www.knowledgehub.org.za/content/standard-treatment-guidelines-and-essential-medicines-list

[xxii] Medical abortion (follow-up pregnancy test): NICE. Guideline: Abortion Care, 25 September 2019. https://www.nice.org.uk/guidance/ng140

Medical abortion (follow-up pregnancy test): Barnhart K, Sammel MD, Chung K, Zhou L, Hummel AC, Guo W. Decline of serum human chorionic gonadotropin and spontaneous complete abortion: defining the normal curve. Obstet Gynecol. 2004 Nov;104(5 Pt 1):975–81. https://pubmed.ncbi.nlm.nih.gov/15516387/

[xxiii] Misoprostol - doses (2nd trimester: incomplete miscarriage): Morris JL, Winikoff B, Dabash R, Weeks A, Faundes A, Gemzell-Danielsson K, Kapp N, Castleman L, Kim C, Ho PC, Visser GHA. FIGO's updated recommendations for misoprostol used alone in gynecology and obstetrics. Int J Gynaecol Obstet. 2017 Sep;138(3):363-366. https://www.ncbi.nlm.nih.gov/pubmed/28643396

[xxiv] Misoprostol - doses (2nd trimester: previous Caeserean section): Dodd JM, Crowther CA. Misoprostol for induction of labour to terminate pregnancy in the second or third trimester for women with a fetal anomaly or after intrauterine fetal death. Cochrane Database Syst Rev. 2010 Apr 14;(4):CD004901. https://www.ncbi.nlm.nih.gov/pubmed/20393941

Misoprostol - doses (2nd trimester: previous Caeserean section): Morris JL, Winikoff B, Dabash R, Weeks A, Faundes A, Gemzell-Danielsson K, Kapp N, Castleman L, Kim C, Ho PC, Visser GHA. FIGO's updated recommendations for misoprostol used alone in gynecology and obstetrics. Int J Gynaecol Obstet. 2017 Sep;138(3):363-366. https://www.ncbi.nlm.nih.gov/pubmed/28643396

[xxv]TOP option (MVA or medical TOP): Blanchard K, Lince-Deroche N, Fetters T, Devjee J, de Menezes ID, Trueman K, Sudhinaraset M, Nkonko E, Moodley J. Introducing medication abortion into public sector facilities in KwaZulu-Natal, South Africa: an operations research study. Contraception. 2015 Oct;92(4):330-8. http://www.ncbi.nlm.nih.gov/pubmed/26162575

[xxvi] Mifepristone, oral (TOP - Up to 12 weeks and 0 days): Zhang J, Zhou K, Shan D, Luo X. Medical methods for first trimester abortion. Cochrane Database Syst Rev. 2022 May 24;5(5):CD002855. https://pubmed.ncbi.nlm.nih.gov/35608608/

Mifepristone, oral (TOP - Up to 12 weeks and 0 days): National Department of Health: Affordable Medicines, EDP-Adult Hospital level. Medicine Review Update: Mifepristone for medical termination of pregnancy, 20 October 2017. https://www.knowledgehub.org.za/e-library

Mifepristone, oral (TOP - Up to 12 weeks and 0 days): The Royal College of Obstetricians and Gynaecologist. Best practice in comprehensive abortion care, June 2015. https://www.rcog.org.uk/globalassets/documents/guidelines/best-practice-papers/best-practice-paper-2.pdf

[xxvii] Misoprostol, oral/PV (TOP - Up to 12 weeks and 0 days): World Health Organisation. Medical management of abortion, 2018. http://www.who.int/reproductivehealth/publications/medical-management-abortion/en/

[xxviii]Morphine, IM: South African Medicines Formulary. 13th Edition. Division of Clinical Pharmacology. University of Cape Town, 2020.

[xxix]Lidocaine 1% (paracervical block): Renner RM, Nichols MD, Jensen JT, Li H, Edelman AB. Paracervical block for pain control in first-trimester surgical abortion: a randomized controlled trial. Obstet Gynecol. 2012 May;119(5):1030-7. https://www.ncbi.nlm.nih.gov/pubmed/22525915

[xxx] Medical TOP (12-20 weeks): World Health Organisation. Safe abortion: technical and policy guidance for health systems,

2012. http://www.who.int/reproductivehealth/publications/unsafe_abortion/9789241548434/en/
[xxxi] Medical TOP (12-20 weeks): National guideline for implementation of the choice on TOP ACT 2020, page 19.
[xxxii] Mifepristone, oral (TOP - 2nd trimester): Wildschut H, Both MI, Medema S, Thomee E, Wildhagen MF, Kapp N. Medical methods for mid-trimester termination of pregnancy. Cochrane Database Syst Rev. 2011 Jan 19;(1):CD005216. https://www.ncbi.nlm.nih.gov/pubmed/21249669
Mifepristone, oral (TOP - 2nd trimester): National Department of Health: Affordable Medicines, EDP-Adult Hospital level. Medicine Review Update: Mifepristone for medical termination of pregnancy, 20 October 2017. https://www.knowledgehub.org.za/content/standard-treatment-guidelines-and-essential-medicines-list
Mifepristone, oral (TOP – 2nd trimester): The Royal College of Obstetricians and Gynaecologist. Best practice in comprehensive abortion care, June 2015. https://www.rcog.org.uk/globalassets/documents/guidelines/best-practice-papers/best-practice-paper-2.pdf
[xxxiii] Interval between mifepristone-misoprostol (12-24 hours for 2nd trimester TOP): Shaw KA, Topp NJ, Shaw JG, Blumenthal PD. Mifepristone-misoprostol dosing interval and effect on induction abortion times: a systematic review. Obstet Gynecol. 2013 Jun;121(6):1335-47. https://www.ncbi.nlm.nih.gov/pubmed/23812471
[xxxiv] Misoprostol, PV/SL/buccal (2nd trimester TOP): World Health Organisation. Medical management of abortion, 2018. http://www.who.int/reproductivehealth/publications/medical-management-abortion/en/
[xxxv] Copper IUD (emergency contraception): Turok DK, Jacobson JC, Dermish AI, Simonsen SE, Gurtcheff S, McFadden M, Murphy PA. Emergency contraception with a copper IUD or oral levonorgestrel: an observational study of 1-year pregnancy rates. Contraception. 2014 Mar;89(3):222-8. https://pubmed.ncbi.nlm.nih.gov/24332433/
Copper IUD (emergency contraception): FSRH Guideline (April 2019) Overweight, Obesity and Contraception. BMJ Sex Reprod Health. 2019 Apr;45(Suppl 2):1-69. https://pubmed.ncbi.nlm.nih.gov/31053605/
[xxxvi] Levonorgestrel 1.5 mg oral (emergency contraception): Shen J, Che Y, Showell E, Chen K, Cheng L. Interventions for emergency contraception. Cochrane Database Syst Rev. 2019 Jan 20;1(1):CD001324. https://pubmed.ncbi.nlm.nih.gov/30661244/
[xxxvii] Levonorgesterol, oral - emergency contraception (double dose): Carten ML, Kiser JJ, Kwara A, Mawhinney S, Cu-Uvin S. Pharmacokinetic interactions between the hormonal emergency contraception, levonorgestrel (Plan B), and Efavirenz. Infect Dis Obstet Gynecol. 2012;2012:137192. http://www.ncbi.nlm.nih.gov/pubmed/22536010
Levonorgesterol, oral - emergency contraception (double dose): Tittle V, Bull L, Boffito M, Nwokolo N. Pharmacokinetic and pharmacodynamic drug interactions between antiretrovirals and oral contraceptives. ClinPharmacokinet. 2015 Jan;54(1):23-34. http://www.ncbi.nlm.nih.gov/pubmed/25331712
Levonorgesterol, oral - emergency contraception (double dose): Jatlaoui TC and Curtis KM. Safety and effectiveness data for emergency contraceptive pills among women with obesity: a systematic review. Contraception 94 (2016) 605–611. https://www.ncbi.nlm.nih.gov/pubmed/27234874
Levonorgesterol, oral - emergency contraception (double dose): FSRH Guideline (April 2019) Overweight, Obesity and Contraception. BMJ Sex Reprod Health. 2019 Apr;45(Suppl 2):1-69. https://pubmed.ncbi.nlm.nih.gov/31053605/
[xxxviii] STI prophylaxis: STI prophylaxis: Workowski KA, Bachmann LH, Chan PA, Johnston CM, Muzny CA, Park I, Reno H, Zenilman JM, Bolan GA. Sexually Transmitted Infections Treatment Guidelines, 2021. MMWR Recomm Rep. 2021 Jul 23;70(4):1-187. https://pubmed.ncbi.nlm.nih.gov/34292926/
[xxxix] Fluoxetine, oral: National Department of Health: Affordable Medicines, EDP-Adult Hospital level. Medicine Review: SSRIs for control of menopausal symptoms in women where hormone therapy is contra-indicated, July 2018. https://www.knowledgehub.org.za/content/standard-treatment-guidelines-and-essential-medicines-list
Fluoxetine, oral: Grant MD, Marbella A, Wang AT, Pines E, Hoag J, Bonnell C, et al. Menopausal Symptoms: Comparative Effectiveness of Therapies [Internet]. Rockville (MD): Agency for Healthcare Research and Quality (US); 2015 [cited 2018 Aug 30]. (AHRQ Comparative Effectiveness Reviews). Available from: http://www.ncbi.nlm.nih.gov/books/NBK285463/
[xl] Citalopram, oral (concomitant tamoxifen): National Department of Health: Affordable Medicines, EDP-Adult Hospital level. Medicine Review: SSRIs for control of menopausal symptoms in women where hormone therapy is contra-indicated, July 2018. https://www.knowledgehub.org.za/content/standard-treatment-guidelines-and-essential-medicines-list
Citalopram, oral (concomitant tamoxifen): Grant MD, Marbella A, Wang AT, Pines E, Hoag J, Bonnell C, et al. Menopausal Symptoms: Comparative Effectiveness of Therapies [Internet]. Rockville (MD): Agency for Healthcare Research and Quality (US); 2015 [cited 2018 Aug 30]. (AHRQ Comparative Effectiveness Reviews). Available from: http://www.ncbi.nlm.nih.gov/books/NBK285463/
Citalopram, oral (concomitant tamoxifen): Davari-Tanha F, Soleymani-Farsani M, Asadi M, Shariat M, Shirazi M, Hadizadeh H. Comparison of citalopram and venlafaxine's role in treating sleep disturbances in menopausal women, a randomized, double-blind, placebo-controlled trial. Arch Gynecol Obstet. 2016 May;293(5):1007–13. https://www.ncbi.nlm.nih.gov/pubmed/26437957
[xli] Management of ectopic pregnancy and miscarriage: Practice Committee of American Society for Reproductive Medicine. Medical treatment of ectopic pregnancy: a committee opinion. Fertil Steril. 2013 Sep;100(3):638-44. https://www.ncbi.nlm.nih.gov/pubmed/23849842
[xlii] Methotrexate, IM (Single dose protocol for ectopic pregnancy): Hajenius PJ, Mol F, Mol BW, Bossuyt PM, Ankum WM, van der Veen F. Interventions for tubal ectopic pregnancy. Cochrane Database Syst Rev. 2007 Jan 24;(1):CD000324. https://www.ncbi.nlm.nih.gov/pubmed/17253448
[xliii] Methotrexate, IM: Ectopic pregnancy and miscarriage: diagnosis and initial management in early pregnancy of ectopic pregnancy and miscarriage. National Guideline Clearinghouse [Internet]. [cited 2017 Jun 8]. Available from: https://guideline.gov/summaries/summary/39274/ectopic-pregnancy-and-miscarriage-diagnosis-and-initial-management-in-early-pregnancy-of-ectopic-pregnancy-and-miscarriage?q=ectopic+pregnancy.
Methotrexate, IM: Diagnosis and Management of Ectopic Pregnancy [Internet]. Royal College of Obstetricians & Gynaecologists. [cited 2017 Jun 8]. Available from: https://www.rcog.org.uk/en/guidelines-research-services/guidelines/gtg21/
[xliv] Methotrexate, IM (caution): Joint Formulary Committee. British National Formulary. 80. London: BMJ Group and Pharmaceutical Press; 2020.

[xlv] NSAIDs (bleeding associated with IUCDs): Grimes DA, Hubacher D, Lopez LM, Schulz KF. Non-steroidal anti-inflammatory drugs for heavy bleeding or pain associated with intrauterine-device use. Cochrane Database Syst Rev. 2006 Oct 18;(4):CD006034. https://www.ncbi.nlm.nih.gov/pubmed/17054271

[xlvi] NSAIDs (bleeding associated with injectable progestins): National Department of Health. National Contraception and Fertility Planning and Service Delivery Guidelines, 2019. https://www.knowledgehub.org.za/content/standard-treatment-guidelines-and-essential-medicines-list

[xlvii] Tranexamic acid, oral (bleeding associated with injectable progestins): Bryant-Smith AC, Lethaby A, Farquhar C, Hickey M. Antifibrinolytics for heavy menstrual bleeding. Cochrane Database Syst Rev. 2018 Apr 15;4(4):CD000249 https://pubmed.ncbi.nlm.nih.gov/29656433/

CHAPTER 6
OBSTETRICS

Note: For medical complications during pregnancy, refer to the relevant chapters. Only common conditions specific to pregnancy or requiring special management in pregnancy are included in this chapter.

6.1 ANAEMIA IN PREGNANCY

O99.0 + (D50.9/D64.9)

DESCRIPTION

Haemoglobin (Hb) <11 g/dL. Anaemia in pregnancy is most commonly due to iron deficiency. Hb levels in pregnancy should be checked routinely on-site at the first antenatal visit, and again at 30 weeks and 38 weeks. If Hb falls below 10 g/dL, commence treatment with iron and do a FBC.

LoE:IVb[i]

GENERAL MEASURES

A balanced diet to prevent nutritional deficiency.
Advise against eating soil, clay, charcoal, and excessive consumption of tea and coffee.

MEDICINE TREATMENT

Prophylaxis Z34.9 + (Z29.9)

- Ferrous sulfate compound BPC (dried), oral, 170 mg (± 55 mg elemental iron) twice daily.

OR

- Ferrous fumarate, oral, 200 mg (± 65 mg elemental iron) daily.

LoE:IVb[ii]

<u>If daily iron is poorly tolerated (e.g., epigastric pain, nausea, vomiting, and constipation), intermittent iron supplementation may be administered:</u>

- Ferrous sulfate compound BPC (dried), oral, 340 mg per week, (± 110 mg elemental iron), with meals.

LoE:IVb[iii]

OR

- Ferrous fumarate, oral, 400 mg per week (± 130 mg elemental iron).

(For folic acid supplementation guidance to prevent neural tube defects, Primary Health Care STGs and EML, Section 6.4.1: Antenatal supplements.)

Treatment: Iron deficiency (Hb <10 g/dL)

- Ferrous sulfate compound BPC, oral (dried), 170 mg (± 55 mg elemental iron) 12 hourly.

LoE:IIb[iv]

OR

- Ferrous fumarate, oral, 200 mg (± 65 mg elemental iron) 12 hourly.
  - Continue for 3-6 months after Hb reaches normal to replenish iron stores.
  - Hb is expected to rise by at least 1.5 g/dL in two weeks.
  - When using iron together with calcium supplementation, ensure that iron and calcium are taken at least 4 hours apart from one another.
  - If Hb has not increased after 4 weeks of therapy, do a FBC to confirm hypochromic microcytic anaemia.

LoE:IIIb[v]

Parenteral iron - See Section: 2.1.1 Anaemia, iron deficiency.
If there is no response to oral iron, and iron deficiency is confirmed, review adherence to oral iron, and consider:

- Iron, IV, e.g.:
- Iron sucrose, IV, 200 mg in 200 mL sodium chloride 0.9%, over 30 minutes, given on alternate days until the total dose has been given**.**
  - **Note:** Test dose is not required but administer only where personnel and therapies are readily available to manage anaphylactic-type reactions.
  - An initial total dose of 600 mg is usually adequate to raise the Hb to acceptable levels.
  - For markedly anaemic or very obese women, consult the package insert on the total dose of iron infusion.

LoE:IVb

REFERRAL/CONSULTATION

No response to management.

6.2 DIABETES MELLITUS IN PREGNANCY

O24.0-4/O24.9

This condition should ideally be managed in consultation with a specialist.

DESCRIPTION

Established diabetes: Diabetes (type 1 or 2) predating pregnancy.
Gestational diabetes mellitus (GDM): carbohydrate intolerance first recognised during pregnancy. It does not exclude the possibility that diabetes preceded the pregnancy.

Diagnostic criteria for GDM

Either a fasting plasma glucose ≥5.6 mmol/L **OR** a plasma glucose of ≥7.8 mmol/L two hours after a 75 g oral glucose tolerance test.

The following women should be screened for GDM, between 24 and 28 weeks of gestation:

» Women of Indian ethnic origin.
» BMI >35 kg/m^2.
» Age >40 years of age.
» GDM in previous pregnancy.

» Family history (first degree relative) of diabetes.
» Previous unexplained third trimester fetal death.
» Previous baby with birthweight >4.5 kg.
» Polyhydramnios in index pregnancy.
» Glycosuria (≥1+ glucose in urine on 2 or more occasions).
» A fetus that is large for gestational age. LoE:IIIb[vi]

GENERAL MEASURES

» Stop smoking.
» Moderate exercise.
» Dietary advice.

Elective delivery at about 38 weeks' gestation.

MEDICINE TREATMENT

If fasting glucose is <7 mmol/l at diagnosis, promote lifestyle changes (diet and moderate exercise).
Assess after 2 weeks. LoE:IIIb[vii]

Fasting glucose ≥7 mmol/l, or no response to lifestyle changes:

- Metformin, oral, 500 mg daily.
  - Increase dose to 500 mg 12 hourly after 7 days.
  - Titrate dose to a maximum of 850 mg 8 hourly according to glucose control.
  - Contra-indications to metformin: liver or renal impairment.
  - If not tolerated, change to insulin.

Do capillary (finger prick) glucose profiles, i.e. pre-prandial and 1-hour or 2-hour (2-hours more practical) post-prandial for breakfast, lunch and supper.
Aim for:

» Preprandial level <5.3 mmol/L and either:
  - 1-hour postprandial <7.8 mmol/L, or
  - 2-hour postprandial <6.4 mmol/L.

Abnormal profiles LoE:IVb[viii]

Women with diabetes treated with metformin but with poor glucose control should be admitted.
Add insulin.
Insulin requirements may increase with increasing gestation and later readmission may be necessary.

Preferred insulin regimen

- Insulin, short-acting with all 3 meals to maintain the 2-hour postprandial glucose levels <6.4 mmol/L.

AND

- Insulin, intermediate acting at bedtime (with a bedtime snack) to maintain the fasting (morning) preprandial glucose levels <5.3 mmol/L.

Insulin dosing (in addition to metformin):

- Total daily dose: SC, 0.1 units/kg/day.
- One third of the total dose: intermediate acting insulin at bedtime.
- The remaining two thirds divided into three equal doses: short-acting insulin given before each meal (breakfast, lunch and supper).
- Adjust insulin dosage daily according to blood glucose profiles, until control is adequate.

LoE:IIIb[ix]

Where the above recommended regimen is not feasible

Twice-daily regimen with biphasic insulin.

- Insulin, biphasic.
  - Daily dose: SC, 0.5 units/kg/day, two thirds, 30 minutes before breakfast and one third 30 minutes before supper.
  - Titrate to achieve target capillary (finger prick) glucose as above.

LoE:IIb[x]

Delivery

Plan induction of labour at 38 weeks' gestation, provided glucose control is adequate, or earlier with maternal co-morbid conditions, or if glycaemic control is poor. If the estimated fetal weight (EFW) on ultrasound is >4 kg, offer elective Caesarean delivery.

During labour:

Monitor glucose hourly.

Stop subcutaneous insulin.

Administer short-acting insulin to maintain physiological blood glucose levels.

- Insulin, short-acting, continuous IV infusion, 20 units plus 20 mmol potassium chloride in 1 L dextrose 5% at an infusion rate of 50 mL/hour, i.e. 1 unit of insulin/hour.
  - If blood glucose <4 mmol/L, discontinue insulin.
  - If >7 mmol/L, increase infusion rate to 100 mL/hour.

Postpartum insulin requirements decrease rapidly.

During the first 48 hours give insulin 4-hourly according to blood glucose levels.

Resume pre-pregnancy insulin or oral hypoglycaemic regimen once eating a full diet.

The newborn is at risk of:

- » hypoglycaemia
- » respiratory distress syndrome
- » hyperbilirubinaemia
- » congenital abnormalities

Postpartum management

Contraception Z30.0 + (O24.3-4/O24.9)

Tubal ligation should be considered.

Consider:

- Low-dose combined contraceptive in well-controlled cases.
- Progestin-only preparation **or** intra-uterine contraceptive device if planning to breastfeed.

See PHC Chapter 7: Family planning.

Need for ongoing anti-diabetic therapy
Offer women diagnosed with GDM during the index pregnancy an oral glucose tolerance test after 6 weeks postpartum to assess whether they have diabetes needing ongoing therapy.

REFERRAL/CONSULTATION
» Obese women (BMI > 40 kg/m^2)
» Excessive fetal growth despite adequate diabetes control.
» Poor glucose control despite adequate insulin.

6.3 HEART DISEASE IN PREGNANCY
O99.4 + (I51.9)

All women with heart disease require referral for specialist evaluation and risk assessment. The risk is particularly high in women with mechanical valves, Eisenmenger's syndrome or pulmonary hypertension. Termination of pregnancy (TOP) is an option for women with severe heart disease if recommended by a specialist.

GENERAL MEASURES
All pregnant women with haemodynamically significant heart disease require multidisciplinary management in consultation with both obstetrician and physician/cardiologist.
Consider thyrotoxicosis, anaemia, and infection, which may precipitate cardiac failure.
Spontaneous delivery is usually preferable to Caesarean delivery, unless there are obstetric reasons for surgery.
Women with prosthetic heart valves should be counselled about the risks of pregnancy to themselves and their fetus; and offered effective contraception.

During labour:
» Nurse in semi-Fowler's position.
» Avoid unnecessary intravenous fluids.
» Give adequate analgesia.
» Give antibiotic prophylaxis for infective endocarditis, guided by the nature of the heart lesion (for cardiac indications and antibiotic recommendations see Section 3.5: Endocarditis, Infective). Procedures for which endocarditis prophylaxis is indicated include:
  – Vaginal delivery in the presence of suspected infection.
  – Caesarean delivery.
  – Assisted vaginal delivery.
  – Prelabour rupture of membranes.
» Avoid a prolonged second stage of labour by means of assisted delivery with forceps (preferably) or ventouse.
» Avoid ergometrine after delivery of the newborn.

» Observe in a high care area for 24 hours post-delivery, as the risk of pulmonary oedema is highest in this period.

Contraception, including the option of tubal ligation should be discussed during the antenatal period and after delivery in all women with significant heart disease.
Women who had life-threatening complications during pregnancy should be advised not to become pregnant again.

Anticoagulation during pregnancy:
Indications for full anticoagulation during pregnancy (high risk):

» *Valvular disease with atrial fibrillation*: Women with valvular heart disease should be guided to consider completing their family early and then consider family planning including tubal ligation, before progressing to requiring mechanical valves.
» *Mechanical prosthetic heart valves:* Women with mechanical prosthetic heart valves should be offered contraception (preferably a LARC not containing estrogen); see PHC Chapter 7: Family planning. If they conceive, offer the option of TOP or refer to tertiary centre for anticoagulation management by a multi-disciplinary team.

MEDICINE TREATMENT

A. Thromboprophylaxis for pregnant women with valvular disease and atrial fibrillation:

1. First trimester

- Enoxaparin SC, 1 mg/kg 12 hourly.

OR

- Unfractionated heparin, IV, 5 000 units as a bolus.
  - Followed by 1 000–1 200 units/hour as an infusion.

OR

- Unfractionated heparin, SC, 15 000 units 12 hourly.
  - Adjust the dose to achieve a mid-target PTT at 2–3 x control.

Practise strict infection control if using multi-dose vials, with one vial per patient and use of needle-free adaptor.

2. Second trimester until 36 weeks

- Warfarin, oral, 5 mg daily.
  - Adjust dose to keep INR within the therapeutic range of 2–3.

3. After 36 weeks until delivery

- Enoxaparin SC, 1 mg/kg 12 hourly.

OR

- Unfractionated heparin, IV, 5 000 units as a bolus.
  - Followed by 1 000–1 200 units/hour as an infusion.

OR

- Unfractionated heparin, SC, 15 000 units 12 hourly.
  - Adjust dose to keep aPTT 2–3 x control.

4. Delivery

Stop heparin on the morning of elective Caesarean delivery (6 hours before scheduled surgery) or when in established labour, and re-start 6 hours after vaginal delivery or 12 hours after Caesarean delivery, as long as there is no concern that the patient is bleeding.

Secondary prophylaxis for venous thromboembolism - see Chapter 2: Blood and blood forming organs, Section 2.8.3: VTE during pregnancy and the puerperium.

B. Cardiac failure during pregnancy O99.4 + (I50.9)

See Section 3.4: Congestive Cardiac Failure (CCF).

Treatment is as for non-pregnant women, except that **ACE-inhibitors, ARBs and spironolactone are contra-indicated.** *LoE:IVb*[xi]

If a vasodilator is needed:

- Hydralazine, oral, 25 mg 8 hourly.
  - Maximum dose: 200 mg daily.

AND

- Isosorbide dinitrate, oral, 20 mg 12 hourly.
  - Maximum dose: 160 mg daily.

C. Delivery by a cardiac patient O99.4 + (I51.9)

Contraction and retraction of the uterus after delivery increases the total peripheral resistance and causes a relative increase in circulating volume. This may precipitate pulmonary oedema.

In women with NYHA grade II dyspnoea or more, consider the use of furosemide:

- Furosemide, IV, 40 mg with delivery of the baby.
  - Monitor for 48 hours thereafter for pulmonary oedema.

REFERRAL

» All pregnant women with mechanical prosthetic heart valves requiring anticoagulation.

Pregnant women with mechanical prosthetic valves should not receive LMWH unless antifactor Xa levels can be monitored reliably weekly. Therapeutic range is pre-dosing level 0.6 units/mL and a 4-hour peak level of 1–1.2 units/mL

6.4 HYPERTENSIVE DISORDERS IN PREGNANCY

O10.0/O11/O14.0-2/O14.9/O16

DESCRIPTION

Hypertensive disorders are one of the most common direct causes of maternal mortality and are responsible for significant perinatal and maternal morbidity. These disorders include chronic hypertension, pre-eclampsia, eclampsia and HELLP Syndrome. Early detection and timely intervention is essential to prevent maternal and perinatal complications.

GENERAL MEASURES

Bed rest, preferably in hospital.
Lifestyle adjustment and diet.
Monitor BP, urine output, renal and liver function tests, platelet count, proteinuria, and fetal condition.
Consider delivery when risks to mother outweigh risks of prematurity to baby.

MEDICINE TREATMENT

Treatment

Antihypertensives

Medicine treatment will be dictated by blood pressure response.
Monitor progress until a stable result is achieved.
In general, diuretics are contra-indicated for hypertension in pregnant women.
When needed, combine drugs using lower doses when BP >160/100 mmHg, before increasing single medication doses to a maximum.

- Methyldopa, oral, 250 mg 8 hourly as a starting dose. *LoE:IVb*[xii]
  - Increase to a maximum of 750 mg 8 hourly, according to response.

AND/OR

- Long-acting calcium channel blocker, e.g.:
- Amlodipine, oral, 5 mg daily.
  - Increase to 10 mg daily. *LoE:IIb*[xiii]

Preeclampsia

Preeclampsia is defined as hypertension with significant proteinuria developing for the first time after 20 weeks' gestation and can also be superimposed on chronic hypertension - evidenced by the new onset (after 20 weeks' gestation) of persistent proteinuria in a woman who had an initial diagnosis of chronic hypertension.

Pre-eclampsia without severe features:

A diastolic BP of 90-109 mmHg and/or systolic BP of 140-159 mmHg; but no symptoms or organ dysfunction.

Maternal features of severe disease:

» Acute severe hypertension (diastolic BP ≥ 110 mmHg and/or systolic ≥160 mmHg).

» Thrombocytopenia (platelet <100 000/µL).
» Impaired liver function (ALT or AST >40 IU/L).
» Severe persistent right upper quadrant or epigastric pain.
» HELLP syndrome (platelets <100 000 and AST >70 U/L and LDH >600 U/L).
» Serum creatinine ≥120 micromol/L.
» Pulmonary oedema.
» New-onset severe headache unresponsive to medication.
» Visual disturbances.

Hypertensive emergency O10.0/9
SBP ≥160 mmHg and/or DBP ≥110 mmHg. Admit to a high care setting for close monitoring.

- Nifedipine, oral, 10 mg.
  - Repeat after 30 minutes if needed, until systolic blood pressure <160 mmHg and diastolic blood pressure <110 mmHg.
  - Swallow whole. Do not chew, bite or give sublingually.

If unable to take oral or inadequate response:

LoE:IIIb[xiv]

- Labetalol, IV infusion, 2 mg/minute to a total of 1–2 mg/kg.
  - Reconstitute solution as follows:
    - Discard 40 mL of sodium chloride 0.9% from a 200 mL container.
    - Add 2 vials (2 x 100 mg) of labetalol (5 mg/mL) to the remaining 160 mL of sodium chloride 0.9% to create a solution of 1 mg/mL.
    - Start at 40mL/hour to a maximum of 160 mL/hour.
    - Titrate against BP – aim for BP of 140/100 mmHg.
  - Once hypertensive crisis has resolved, switch to an oral preparation.

Delivery

LoE:Ia[xv]

- Oxytocin, IM, 10 units as a single bolus after delivery of the baby.

LoE:IVb[xvi]

Ergot-containing medicines are contraindicated in hypertensive women, including pre-eclampsia, following delivery of the baby.
Pre-eclamptic and eclamptic women are often hypovolaemic, particularly when the haematocrit exceeds 40%, but are also susceptible to pulmonary oedema. Consequently, hypotension is a risk during anaesthesia. Careful infusion of IV fluids is important. Limit blood-loss at Caesarean section.

6.4.1 PREECLAMPSIA

O11/O14.0-2/O14.9

DESCRIPTION

Preeclampsia is defined as hypertension with significant proteinuria developing for the first time after 20 weeks' gestation and can also be superimposed on chronic hypertension - evidenced by the new onset (after 20 weeks' gestation) of persistent proteinuria in a woman who had an initial diagnosis of chronic hypertension.

Pre-eclampsia without severe features:
A diastolic BP of 90-109 mmHg and/or systolic BP of 140-159 mmHg; but no symptoms or organ dysfunction.

Maternal features of severe disease:
» Acute severe hypertension (diastolic BP ≥ 110 mmHg and/or systolic ≥160 mmHg).
» Thrombocytopenia (platelet <100 000/µL).
» Impaired liver function (ALT or AST >40 U/L).
» Severe persistent right upper quadrant or epigastric pain.
» HELLP syndrome (platelets <100 000 and AST >70 U/L and LDH >600 U/L).
» Serum creatinine ≥120 micromol/L.
» Pulmonary oedema.
» New-onset severe headache unresponsive to medication.
» Visual disturbances.

Prevention of pre-eclampsia Z29.2 + O10.0/O24.0-3/O99.1/O99.8 + (D68.6/M32.9)
For women at high risk of pre-eclampsia, e.g. pre-eclampsia in a previous pregnancy, chronic hypertension, diabetes, antiphospholipid syndrome, or SLE.

From 6 weeks' gestation onwards, preferably starting before 16 weeks' gestation:
- Aspirin, oral, 150 mg daily until 36 weeks. *LoE:Ia*[xvii]

At confirmation of pregnancy
- Calcium, oral.
  - For high-risk patients: Calcium (elemental), oral, 1 gram daily.
  - Although the benefit is greatest in high-risk women, consider use of this agent in all pregnant women.
  - When using iron together with calcium supplementation, ensure that iron and calcium are taken at least 4 hours apart from one another.

LoE:Ia[xviii]

Prevention of eclampsia
To prevent eclamptic seizures, magnesium sulfate is recommended for patients with severe features. In some cases, this allows for delivery to be delayed to improve neonatal outcome. When used for prevention of eclampsia, magnesium sulfate is administered for 24 hours and then stopped. The same dose regimens are used as for eclampsia. Women with severe features should be managed under specialist care.

6.4.2 ECLAMPSIA

O15.0-2/O15.9

DESCRIPTION

Generalised tonic-clonic seizures after 20 weeks of pregnancy or within 7 days after delivery associated with hypertension and proteinuria. Exclude any other obvious cause of the seizure before making the diagnosis. Management will include preventing further seizures, controlling the blood pressure, referral to a high-care unit, and delivery of the baby if not already post-delivery.

GENERAL MEASURES

Place patient in left-lateral position.
Clear airway. If necessary, insert oropharyngeal airway.
Abort seizures with magnesium sulfate.

MEDICINE TREATMENT

If necessary:

- Oxygen via nasal prongs or face mask to maintain a saturation of >90%.

Treatment

Where infusion pumps are not available:

- Magnesium sulfate, IV, 4 g in 200 mL sodium chloride 0.9% over 20 minutes.

Follow with:

- Magnesium sulfate, IM, 5 g every 4 hours administered at different sites, until 24 hours after delivery or following the last convulsion.

In high-care setting:

- Magnesium sulfate, IV, 4 g in 200 mL sodium chloride 0.9% over 20 minutes (loading dose).

Follow with:

- Magnesium sulfate, IV infusion, 1 g every hour, until 24 hours after delivery, or after the last convulsion (maintenance dose).

STOP MAGNESIUM SULFATE IF KNEE REFLEXES BECOME ABSENT OR IF URINE OUTPUT <100 ML/ 4 HOURS OR RESPIRATORY RATE <16 BREATHS/MINUTE.

IF RESPIRATORY DEPRESSION OCCURS:

- Calcium gluconate 10%, IV, 10 mL given slowly at a rate not exceeding 5 mL/minute.

Recurrent eclamptic seizure despite magnesium sulfate loading dose administration:

- Magnesium sulfate, IV, 2 g over 10 minutes.

For agitated and restless women with eclampsia:

- Lorazepam, IV/IM, 4 mg.
  - May be repeated after 10-15 minutes.

- Maximum dose: 8 mg.

OR

Clonazepam, IV, 2 mg.

- May be repeated after 5 minutes.
- Maximum dose: 4 mg.

OR

If above not available:

Diazepam, IV, 10–20 mg, not faster than 2 mg/minute.

Notify the person who will resuscitate the newborn that a benzodiazepine and/or magnesium has been given to the mother.

REFERRAL

Refer all eclampsia cases to a high or intensive care facility.

6.4.3 CHRONIC HYPERTENSION

O10.0-4/O10.9

GENERAL MEASURES

Lifestyle modification

» No alcohol should be taken.
» Regular moderate exercise, e.g. 30 minutes brisk walking at least 3 times a week.
» Smoking cessation.
» Aim to keep BP <140/90 mmHg.

Screen for end-organ damage.
Fetal surveillance by symphysis-fundus height (SFH) growth. Umbilical artery Doppler screening (where available) at 24-26 weeks.
Ask mother about fetal movements at each antenatal visit. *LoE:IIb*[xix]

Consider labour induction if:

» BP persistently ≥160/110 mmHg, or
» pregnancy of ≥38 weeks duration, or
» in the presence of maternal or fetal compromise, e.g., poor SFH growth and oligohydramnios, etc.

MEDICINE TREATMENT

See prevention and treatment of pre-eclampsia.

Switch ACE-inhibitors and diuretics to methyldopa and/or amlodipine. Women should be advised that there is an increased risk of congenital abnormalities if ACE-inhibitors were taken during pregnancy.

6.4.4 GESTATIONAL HYPERTENSION

See to PHC Chapter 6: Obstetrics and gynaecology, Sections 6.4.2.2: Gestational hypertension: no severe features, and 6.4.2.3: Gestational hypertension: with severe features.

6.5 CORONAVIRUS DISEASE-19 (COVID-19) IN PREGNANCY

U07.1/U07.2

*Notifiable medical condition.

ANTENATAL CARE:

» Antenatal care is an essential service and should not be scaled down during lockdown periods.

» Screening and testing criteria for SARS-CoV-2 infection during pregnancy is the same as for the general population.

» Vaccination against COVID-19 and influenza is safe at all gestations of pregnancy and during COVID-19 pandemic it is important that pregnant women take up the COVID-19 and influenza vaccine to reduce their risk of contracting either. (See PHC Section 13.7: Other vaccines.)

» The clinical course and outcome of COVID-19 is not different in pregnancy and most pregnant women who are infected with SARS-CoV-2 will experience only mild or moderate symptoms.

» Up to 75% of infected women in pregnancy may be asymptomatic, and appropriate PPE must be used for all deliveries, regardless of the status of the mother. All pregnant women attending hospital, including women in labour, should wear masks.

» Maternal COVID-19 is associated with an approximately three times greater risk of preterm birth and women should be counselled on warning signs of spontaneous preterm labour. *LoE:IIIb*[xx]

» Risk factors for more severe disease or admission to hospital with COVID-19 include:
  - Obesity (pre-pregnancy BMI >30 kg/m^2). *LoE:IIIb*[xxi]
  - Co-morbidity, such as pre-existing diabetes (see Section 6.2: Diabetes mellitus in pregnancy) and chronic hypertension (see Section 6.4.3: Chronic hypertension).
  - Age >35 years

» SARS-CoV-2 infection is not associated with an increase in the incidence of congenital abnormalities.

THROMBOPROPHYLAXIS:

All pregnant women admitted with confirmed or suspected COVID-19 should be offered prophylactic LMWH or unfractionated heparin for 10 days, unless birth is expected within 12 hours. See Section 2.8: Venous thrombo-embolism.

DELIVERY:

» COVID-19 infection is not an indication for delivery, unless delivery is required as part of maternal resuscitation to improve maternal oxygenation.
» When a woman with COVID-19 presents with spontaneous preterm labour, suppression of labour (to delay delivery in order to administer antenatal corticosteroids) should not be done.
» All women with confirmed or suspected SARS-CoV-2 infection must preferably deliver in a dedicated COVID-19 hospital or ward.

MEDICINE TREATMENT

Observe oxygen saturation measurement hourly.

- Oxygen, if saturation is <94%.

Symptomatic relief of headache:

- Paracetamol, oral, 500 mg to 1 g, 4 to 6 hourly as required (to a maximum of 4 g in 24 hours).
  - Maximum dose: 15 mg/kg/dose.

Note: Avoid morphine analgesia if patient is respiratory compromised.

In pregnant patients who require supplemental oxygen:

» Corticosteroids crosses the placenta and may have long-term deleterious effects on the child.

If corticosteroids are also needed to accelerate fetal lung maturity: See Section 6.11.1: Preterm labour (PTL) and preterm prelabour rupture of membranes (PPROM).

If corticosteroids are not needed for fetal lung maturity:

- Corticosteroids, e.g.:
- Dexamethasone, IV, 6 mg daily for up to 10 days, or until discharge.

If there is a concern over in-utero steroid exposure, use alternative therapy (with less placental transfer):

- Prednisone, oral 40 mg daily, for up to 10 days, or until discharge.
  OR
  Hydrocortisone, IV, 80 mg 12 hourly for up to 10 days, or until discharge.

Anaesthetic: *LoE:IIa*[xxii]

- Spinal anaesthesia is the anaesthetic of choice in the absence of contra-indications. See Section 12.7: Anaesthesia, spinal (intrathecal). The patient

should wear a surgical facemask for the duration of the perioperative period.

POSTPARTUM:

» Infection with SARS-CoV-2 is not a contra-indication to breast feeding.
» There is no contra-indication to the use of post-partum contraception. (See PHC Chapter 7: Family planning.)

6.6 HIV IN PREGNANCY

O98.7 + (Z21/B24)

Consult the most recent National Department of Health Guideline for Vertical Transmission Prevention of Communicable Infections

All pregnant women should receive routine counselling and voluntary HIV testing at their very first antenatal visit.

All women who test negative or who decline testing, should be offered repeat HIV testing at every routine visit throughout pregnancy (8 visits in all), at labour/delivery, at the 6-week EPI visit, and three monthly throughout breastfeeding.

WLHIV should be clinically staged and have a blood sample taken for CD4 cell count and serum creatinine on the same day as diagnosis. The results must be obtained within a week.
Initiate lifelong ART in all pregnant or breastfeeding women on the same day of diagnosis regardless of CD4 count or infant feeding practice.

Provide adequate support and counselling, particularly addressing ART adherence.

Discuss postpartum contraceptive use in the antenatal period.

Educate all women during the antenatal period about the benefits of exclusive breastfeeding for the first 6 months and breastfeeding with complimentary feeding from 6 months until at least 2 years after delivery. (Only in circumstance where the mother has confirmed 2nd or 3rd line ART regimen failure (VL >1000 copies/mL), advise not to breastfeed and prescribe replacement feeds.)

Perform a TB symptom screen for all pregnant women at each visit. If any of the answers to the screening questions are positive, do further TB investigations. A TB-NAAT test must be done for all pregnant women with a new diagnosis of HIV disease or known HIV- infected women with a new pregnancy.

Screen and treat all patients for syphilis and other STIs, in line with basic antenatal care.
Test partner for HIV and perform routine cervical cancer screening.

Assist women with unwanted pregnancies <20 weeks' gestation with access to TOP services.

MEDICINE TREATMENT

» Patients should receive ART at the first antenatal visit, whether newly diagnosed or known to be living with HIV but not on ART.

» Tenofovir should not be used in pregnant women with a serum creatinine ≥85 micromol/L (a more sensitive measure of renal impairment in pregnancy than calculated creatinine clearance).

» Pregnant women may be initiated on/switched to a dolutegravir-containing regimen.

LoE:IIb[xxiii]

» Initiate antenatal supplementation (see PHC Section 6.4.1: Antenatal supplements), noting that calcium and DTG should not be taken together on an empty stomach, but can be taken together with food.

1st ANC visit	
Pregnant women not on ART, with normal renal function, **without** TB.	• TDF, oral, 300 mg daily. **AND** • 3TC, oral, 300 mg daily. **AND** • DTG, oral, 50 mg daily. Provided as a fixed dose combination (FDC).
Pregnant women not on ART, with normal renal function, **with** TB. (DTG requires boosting with TB treatment.)	• TDF, oral, 300 mg daily. **AND** • 3TC, oral, 300 mg daily. **AND** • DTG, oral, 50 mg daily. Provided as a fixed dose combination (FDC). **WITH** DTG, oral 50 mg 12 hours later.
Pregnant woman on TDF + FTC + EFV.	Switch to TDF+3TC+DTG.
Pregnant woman already on ART with a VL between 50-1000 copies/ml.	See Section 10.1: Antiretroviral Therapy.
2nd ANC visit (1 week later)	
Creatinine ≤85 micromol/L.	Continue ART as an FDC
Creatinine >85 micromol/L. (TDF is contraindicated)	Replace TDF with ABC as part of a FDC: • ABC, oral, 600 mg daily **AND** • 3TC, oral, 300 mg daily. **AND** • DTG, oral, 50 mg daily.

LoE:IIIb[xxiv]

Caesarean Delivery (CD):
Provide antibiotic prophylaxis to all pregnant women, including HIV-infected pregnant women prior to surgery (See Chapter 11: Surgical antibiotic prophylaxis).

Women with the following risk factors may be at higher risk of infection post Caesarean delivery:
» Advanced immunosuppression.
» Prolonged rupture of membranes (>18 hours).
» Multiple vaginal examinations during labour (>5 PVs).
» Second stage CD.
Monitor carefully and treat infection appropriately.

HIV-infected pregnant women not on ART undergoing elective Caesarean delivery/or in labour:

- NVP, oral, 200 mg as a single dose.

WITH

- TDF, oral, 300 mg as a single dose.

AND

- 3TC, oral, 300 mg as a single dose.

AND

- DTG, oral, 50 mg as a single dose (as a FDC 4 hours before Caesarean delivery).

Followed by lifelong:

- TDF+3TC+DTG (provided as an FDC).

For management of the HIV-exposed infant, see PHC Section 11.5: The HIV exposed infant.

For more information on HIV management, see Section 10.1: Antiretroviral Therapy.

6.7 SYPHILIS

O98.1

DIAGNOSTIC CRITERIA

Most pregnant women infected with syphilis are asymptomatic.
See PHC Section 12.8: Syphilis serology and treatment.

GENERAL MEASURES

Inform contact(s).

MEDICINE TREATMENT

Mother (treat as either early or late latent/unknown stage of syphilis):

For late latent syphilis or syphilis of unknown duration

- Benzathine benzylpenicillin (depot formulation), IM, 2.4 million units diluted in 6 mL 1% lidocaine without adrenaline (epinephrine), weekly for 3 doses.

Note: If the mother has received <3 doses, treat the baby for congenital syphilis.

For early syphilis *LoE:IIIb*[xxv]

- Benzathine benzylpenicillin (depot formulation), IM, 2.4 million units diluted in 6 mL 1% lidocaine without adrenaline (epinephrine), immediately as a single dose.

Severe penicillin allergy (Z88.0)

For penicillin sensitive pregnant women: penicillin desensitisation.

Perform only in an ICU setting or in a setting where recognition and management of anaphylaxis can be assured. See "How to Use These Guidelines" for detailed information.

Oral penicillin desensitisation protocol

A: Prepare stock solution of oral phenoxymethylpenicillin 250mg/ 5mL and dilutions for steps 1-7 and 8-10.
B: Administer increasing doses of penicillin strictly at 15 minutes intervals.

Step	Medicine mg/mL	Amount to administer (mL)
To make 0.5 mg/mL solution: Add 0.5 mL of stock phenoxymethylpenicillin solution to 49.5 mL water (total volume 50mL).		
1	0.5 mg/mL solution (1000 units/mL)	0.1 mL orally
2		0.2 mL orally
3		0.4 mL orally
4		0.8 mL orally
5		1.6 mL orally
6		3.2 mL orally
7		6.4 mL orally
To make 5 mg/mL solution: Dilute 1 mL of stock phenoxymethylpenicillin solution with 9 mL water (total volume 10mL).		
8	5 mg/mL solution (10000 units/mL)	1.2 mL orally
9		2.4 mL orally
10		4.8 mL orally
Stock phenoxymethylpenicillin 250 mg/5 mL = 50 mg/mL.		
11	50 mg/mL (80000 units/mL)	1.0 mL orally
12		2.0 mL orally
13		4.0 mL orally
14		8.0 mL orally

After step 14, observe for 30 minutes, then administer desired dose of intramuscular penicillin.

Note:

- Repeat desensitisation is not required for subsequent doses of the same treatment course (e.g., to complete 3 doses of benzathine benzylpenicillin for late latent syphilis or syphilis of unknown duration).
- However, second and third doses must be administered in a hospital setting.

Asymptomatic, well baby:
Mother has syphilis and has not been treated, or was only partially treated:

- Benzathine benzylpenicillin (depot formulation), IM, 50 000 units/kg as a single dose into the antero-lateral thigh. A

Symptomatic baby

- Procaine penicillin, IM, 50 000 units/kg daily for 10 days. A (Not for IV use.)

OR

Benzylpenicillin (Penicillin G), IV, 50 000 units/kg, 12 hourly for 10 days. A

6.8 HEPATITIS B IN PREGNANCY

O98.4

DESCRIPTION

Hepatitis B virus (HBV) is transmitted sexually or by percutaneous exposure to infectious body fluids, i.e., blood, saliva, vaginal fluid, and semen. Diagnosis is confirmed serologically by a positive hepatitis B surface antigen (HBsAg).

Screening in pregnancy for HBsAg should ideally be performed in the first trimester. HBeAg positive pregnant women are more infectious than HBsAg positive women, as they have higher rates of HBV replication.

GENERAL MEASURES

Screen sexual contact(s); if they are sero-negative, give hepatitis B vaccination.
All infected patients should be counselled with regard to lifestyle modifications to reduce hepatotoxicity, including alcohol, substance abuse, and co-prescription of herbal and traditional medicines.

MEDICINE TREATMENT

Indications for medical therapy in HIV-negative pregnant women are the same as for non-pregnant adults.

» For management of chronic hepatitis B, **without** chronic HIV infection, see Section 1.2.4.2 Hepatitis B, chronic (non-HIV coinfection).
» For management of chronic hepatitis B **with** chronic HIV infection, see Chapter 10: HIV and AIDS. (ART for women with chronic Hepatitis B should always include ARVs active against hepatitis B.)

Note:
» Ensure normal renal function before starting treatment with TDF (serum creatinine <85 micromol/L or creatinine clearance >60 mL/minute).
» Monitor ALT and HBV DNA viral load at 6 months after commencing treatment.
» An adequate virological response is an HBV DNA VL<2000 IU/mL.

Prevention of perinatal transmission
» Caesarean delivery is reserved for obstetric indications only.
» Delivery should take place in a facility that can offer Hepatitis B vaccination to the baby at birth.
» Administration of ARVs active against HBV from 28 weeks of pregnancy will further reduce risk of vertical transmission.

Pregnant women who are HBsAg/ HBeAg positive and HIV negative
» All HIV negative pregnant women are eligible for HIV Pre-exposure prophylaxis (PrEP) (see PHC STGs and EML, section 11.11: Pre-exposure prophylaxis (PrEP)). TDF, which is included in the oral PrEP regimen, has anti-HBV activity, and will reduce the risk of vertical transmission of HBV.
» Women who are HIV negative and HBsAg positive who decline PrEP must be counselled that TDF will reduce risk of vertical transmission of Hepatitis B to the baby, particularly if HBeAg is positive or HBV viral load is high.
» TDF 300 mg daily should be administered from 28 weeks of pregnancy until birth to women with a high hepatitis viral load (≥200 000 IU/mL), or positive HBeAg, or where HBeAg/viral load result is unavailable at 28 weeks.
» For care of babies born to: (1) mothers with acute hepatitis B infection at the time of delivery, (2) mothers who are HBsAg-positive, or (3) mothers who are HBeAg-positive, see Primary Health Care STGs and EML, section 6.6.5: Hepatitis B exposed infant.
» Obtain infectious disease specialist or internal medicine physician opinion before stopping TDF as there is a risk for postpartum hepatitis flare.
» Consider continued treatment for HBV after delivery where indicated (see Section 1.2.4.2 Hepatitis B, chronic (non-HIV coinfection)).

For Pregnant women who are HBsAg/ HBeAg positive and HIV negative

- TDF, oral, 300 mg daily (from 28 weeks of pregnancy until birth).

LoE:IVb[xxvi]

REFERRAL
» Cirrhosis.
» Liver failure.
» Renal dysfunction (TDF is contraindicated in renal impairment. Tenofovir alafenamide (TAF) should be prescribed in place of TDF).
» Refer all infected babies to a specialist paediatrician for further management.

6.9 JAUNDICE IN PREGNANCY
O26.6

DESCRIPTION
The most common causes of jaundice in pregnancy are not pregnancy specific. They include viral hepatitis, and adverse drug reactions.
Pregnancy-specific causes include:
» intrahepatic cholestasis of pregnancy,
» acute fatty liver of pregnancy (acute yellow atrophy of the liver),
» severe pre-eclampsia or eclampsia, and
» hyperemesis gravidarum.

REFERRAL
All, as certain causes of jaundice in pregnancy have a high mortality.

6.10 HYPEREMESIS GRAVIDARUM
O21.0/1/9

DESCRIPTION
Recurrent vomiting leading to ketosis, generally in the first trimester.
Exclude:
» medical causes, e.g., thyrotoxicosis, and
» molar pregnancy.

GENERAL MEASURES
Counselling.
Frequent small, dry meals.
Avoid fatty and spicy foods.
Restrict oral intake for 24–48 hours but ensure adequate intravenous hydration.

MEDICINE TREATMENT
Correct electrolyte imbalance with IV fluids.

- Pyridoxine, oral, 25 mg 8 hourly.

AND

- Vitamin B complex, IV, 10 mL.

AND

- Promethazine, oral/IM/IV 25 mg 8 hourly as needed.

LoE:IIIb[xxvii]

If no/poor response:

ADD

- Metoclopramide, oral/IV, 10–20 mg 6 hourly as needed.

LoE:IIIb[xxviii]

In refractory cases:

Administer daily until hyperemesis is controlled:

- Dexamethasone, IM/IV, 4–8 mg daily.

AND

- Ondansetron, IV, 4–8 mg over 5 minutes, daily.
  - **Note:** There is uncertainty regarding the safety of ondansetron in the first trimester. Use with caution and only when necessary.

LoE:IIIb[xxix]

6.11 PRETERM LABOUR

6.11.1 PRETERM LABOUR (PTL) AND PRETERM PRELABOUR RUPTURE OF MEMBRANES (PPROM)

O60.0/O42.0-2/O42.9

DESCRIPTION

Preterm: <37 weeks' gestation.
Most problems occur at <34 weeks' gestation.
Confirm ruptured membranes by sterile vaginal speculum.
Preterm labour confirmed by regular uterine contractions with progressive cervical changes.

GENERAL MEASURES

Assess fetal wellbeing.
Estimate fetal weight.
Deliver if chorio-amnionitis suspected.

MEDICINE TREATMENT

If gestation <34 weeks:

Pre-hydrate before administration of nifedipine:

- Sodium chloride 0.9%, IV, 200 mL.

AND

- Nifedipine, oral, 20 mg.
  - If contractions persist, follow with 10 mg after 30 minutes then 10 mg 4 hourly for up to 48 hours.

If gestation <32 weeks and where nifedipine contra-indicated:

- Indomethacin, oral, 50 mg immediately then 25 mg 4 hourly for up to 48 hours.

LoE:Ia[xxx]

Note: Indomethacin may cause oligohydramnios, and its use is associated with a risk of premature closure of the ductus arteriosus. Use only if there is intolerance to nifedipine.

To improve fetal lung maturity at 26–34 weeks: (Z29.2)

- Betamethasone, IM, 12 mg, 2 doses 24 hours apart. *LoE:Ia*[xxxi]

If betamethasone is not available:

- Dexamethasone, IM, 8 mg, 3 doses 8 hours apart. *LoE:Ia*[xxxii]

Note: Corticosteroids are maximally effective about 24 hours after administration of the first dose. Therefore, give as soon as possible following diagnosis of PTL or PPROM.

Antibiotic therapy (Z29.2)

- Ampicillin, IV, 1 g 6 hourly for 48 hours. A

Follow with:

- Amoxicillin, oral, 500 mg 8 hourly for a further 5 days. A

AND

- Azithromycin 1g orally as a single dose. W *LoE:IIIa*[xxxiii]

Severe penicillin allergy: (Z88.0)

- Clindamycin, IV, 600 mg 8 hourly for 48 hours. A

Follow with:

- Clindamycin, oral, 450 mg 8 hourly for a further 5 days. A

AND

- Azithromycin 1g orally as a single dose. W *LoE:IIIa*[xxxiv]

Prepare for appropriate care of preterm infant.

REFERRAL

» Fetus that may require neonatal intensive care, e.g. estimated weight <1.5 kg or gestation <32 weeks.
» Fetus requiring specialised treatment after birth, e.g. surgery.
» Severely ill mother.

6.11.2 PREVENTION OF PRETERM LABOUR (SINGLETON PREGNANCIES ONLY)

Z35.2

DESCRIPTION

Women with a previous spontaneous preterm delivery are at higher risk for preterm delivery in the next pregnancy. In certain high-risk cases, pregnancy may be prolonged by the careful consideration of either cervical cerclage or vaginal progesterone therapy.

The following high-risk women should undergo cervical screening and offered a choice of cerclage or progesterone:

» A history of 2nd trimester miscarriage (between 16 and 26 weeks) suggestive of cervical incompetence: (Painless dilatation with a quick labour, and birth of a live baby or fresh stillbirth) after excluding other causes of mid-trimester losses, e.g. intra-uterine death that required induction, abruptio placentae, fetal abnormalities, polyhydramnios, and medical terminations.
» Previous history of spontaneous preterm birth between 27 and 34 weeks (exclude non-spontaneous causes e.g. iatrogenic delivery for pre-eclampsia, or syphilis). No need to refer previous late preterm deliveries (34-37 weeks).

Do not screen low-risk women routinely, as it is not cost-effective.

GENERAL MEASURES

Cervical length must be measured by a skilled operator using transvaginal ultrasound.
Cervical measurement can be done between 16 and 24 weeks.
A cervical length of ≤25 mm indicates a higher risk for recurrent preterm labour.
Discuss the risks and benefits of both options with the patient to make an informed shared decision of the most appropriate treatment.

MEDICINE TREATMENT

Women should be counselled that 20 cerclage procedures will prevent one preterm delivery (NNT 17 to 20) and that progesterone is successful in 1 out of every 8 cases (NNT 6 to 8), to assist them in making an informed decision.

LoE:IIb[xxxv]

Consider prophylactic vaginal progesterone ***or*** cervical cerclage (MacDonald suture) for women with:

» history of spontaneous preterm birth (27-34 weeks) or mid-trimester loss (16-24 weeks), ***and***
» cervical length ≤ 25 mm confirmed on ultrasound (16-24 weeks).

LoE:IIb[xxxvi]

- Progesterone, PV, 200 mg daily.
  - Stop treatment at 34 weeks and refer to antenatal services at primary level of care for further management.

(**Note**: Vaginal progesterone may be considered for high-risk women with a normal cervix length on ultrasound.)

Consider prophylactic cervical cerclage (MacDonald suture) ***only*** for women with:

» cervical length ≤ 25 mm confirmed on ultrasound (16-24 weeks),

AND

» history of preterm prelabour rupture of membranes (PPROM), ***or***
» history of cervical trauma.

Rescue cerclage:

» If the cervix is already open and the membranes exposed, but unruptured, consider a rescue cervical cerclage (16-27 weeks).

» Do not insert a rescue cerclage if there are contractions, active vaginal bleeding or signs of infection.

Cerclage should be removed at 36 weeks, and thereafter the patient can be referred to antenatal services at primary level of care. LoE:IIb[xxxvii]

REFERRAL
Women with recurrent losses and previous cerclage that tore out (severe cervical trauma), as they may require an abdominal cerclage.

6.12 SUPPRESSION OF LABOUR FOR FETAL DISTRESS
O68.0-3/8-9 + (Z51.2)

DESCRIPTION
Tocolysis is useful to treat fetal distress in labour and to suppress labour in women needing transfer or awaiting Caesarean delivery. Also used prior to external cephalic version.

MEDICINE TREATMENT
- Salbutamol bolus, 250 mcg IV, slowly over 2 minutes.
  - Reconstitute the solution as follows:
    - Add 1 mL (i.e., 0.5 mg/mL) salbutamol to 9 mL sodium chloride 0.9% to make a solution of 50 mcg/mL. Administer 5 mL (250 mcg) of this solution.
    - Monitor pulse. Do not administer if mother has cardiac disease.
    - Place the mother in the left lateral position.
    - If pulse increases >120 bpm, discontinue salbutamol.

LoE:IIb[xxxviii]

6.13 LABOUR INDUCTION
Z35.9/Z51.2

If induction of labour is indicated, for medical reasons, for example pre-eclampsia, diabetes, or post-term pregnancy.

GENERAL MEASURES
Counsel the woman about the risks: failed induction or uterine hyperstimulation syndrome, which may require emergency Caesarean delivery.

Cervix favourable and confirmed HIV-uninfected mother
Artificial rupture of the membranes.

Cervix unfavourable (Bishop score <7)
Extra-amniotic Foley catheter with/without saline infusion:
Pass a Foley catheter with 30 mL bulb through cervix with sterile technique.
Inflate bulb with 50 mL water or sodium chloride 0.9%.
Tape catheter to thigh with light traction.

Alternatively, attach sodium chloride 0.9% 1 L with giving set to catheter, and infuse sodium chloride 0.9% at 50 mL/hour. Remove after 24 hours.

LoE:IVb

MEDICINE TREATMENT

Cervix unfavourable (Bishop score <7)

Extra-amniotic Foley catheter (as above) **PLUS** one of the options below:

Prostaglandins, e.g.: LoE:IIb[xxxix]

- Dinoprostone gel, intravaginally, 1 mg.
  - Repeat after 6 hours.
  - Do not exceed 4 mg.

OR

- Dinoprostone tablets, intravaginally, 1 mg.
  - Repeat after 6 hours.
  - Do not exceed 4 mg. LoE:IIIb[xl]

OR

- Misoprostol, oral, 20 mcg 2 hourly until in labour, or up to 24 hours.
  - Oral misoprostol may be given as freshly made-up solution of one 200 mcg tablet in 200 mL water, i.e., 1 mcg/mL solution. Give 20 mL of this solution 2 hourly.
  - Stop misoprostol administration when in established labour.
  - Maximum 24 hours.
  - Never use oxytocin and misoprostol simultaneously.
  - Misoprostol and other prostaglandins are contraindicated in women with previous Caesarean sections and in grand multiparous women.

LoE:IIIb[xli]

Note:

» Misoprostol in larger doses than indicated here for labour induction at term, may cause uterine rupture.

» Only to be prescribed by a doctor experienced in Maternal Health.

Non-stress test and cardiotocography:

Note: Perform a non-stress test (NST), before starting the induction, and cardiotocography (CTG) within an hour of each dinoprostone insertion, to evaluate the fetal condition during labour induction.

When using oral misoprostol, do a baseline NST before commencing IOL, followed by CTG 4-hourly (prior to every alternate dose).

Repeat CTG once contractions have started, or more frequently only if clinically indicated.

LoE:IVb

Cervix favourable (Bishop score ≥7)

Amniotomy followed 2 hours later by:

- Oxytocin, IV, 2 units in 200 mL sodium chloride 0.9%.

LoE:IIIb[xlii]

- Start at an infusion rate of 12 mL/hour (i.e. 2 milliunits/minute). If absent or inadequate contractions, increase infusion rate according to the table below:

Time after starting (minutes)	Oxytocin dose (milliunits/minute)	Dilution: 2 units in 200 mL sodium chloride 0.9% (mL/hour)
0	2	12
30	4	24
60	6	36
90	8	48
120	10	60
150	12	72
180	14	84
210	16	96
240	18	108
270	20	120

Note:

» It is safe to perform amniotomy in pregnant women living with HIV on ART who have an undetectable plasma VL at delivery.

LoE:IIIb[xliii]

» Avoid oxytocin in women with previous Caesarean section or parity ≥5.
» Continuous electronic fetal heart rate monitoring is essential.
» Aim for adequate uterine contractions (3–5 contractions in 10 minutes). Once adequate contractions achieved, do **not** increase rate further.
» Most women will experience adequate contractions at a dose of 12 milliunits/minute.
» If tachysystole develops (>5 contractions in 10 minutes), reduce or stop the oxytocin infusion to achieve 3-5 contractions in 10 minutes. If there are fetal heart rate abnormalities which persist despite stopping the oxytocin, administer salbutamol as above.

6.14 LABOUR PAIN, SEVERE

O62.9 +(Z51.2)

GENERAL MEASURES

Antenatal counselling.
Psychological support from family member, friend or volunteer ‘doula’.
The need for analgesics may be reduced by keeping the woman informed about the progress of labour, providing reassurance and carefully explaining the procedures performed.
Anticipate the need for analgesia rather than waiting for severe distress.

MEDICINE TREATMENT

- Morphine, IM, 0.1 mg/kg 4 hourly as needed, to a maximum of 10 mg.

Titrate dose and dose frequency according to pain. LoE:IVb[xliv]
Supplement with premixed nitrous oxide 50%/ oxygen 50% in late first stage.

Epidural anaesthesia
Offer this service only at hospitals with anaesthetic expertise, monitoring, capacity and equipment for epidural. (See Chapter 12: Anaesthesiology, and intensive care.)

Perineal analgesia: R10.2

- Lidocaine, 1 or 2%, infiltration, locally or by a pudendal block.

Postpartum and post-episiotomy pain O90.9 + (R10.2 + Z51.2)

- Paracetamol, oral, 500 mg to 1 g, 4 to 6 hourly as required (to a maximum of 4 g in 24 hours).
  - Maximum dose: 15 mg/kg/dose.

OR

- NSAID, e.g.:
- Ibuprofen, oral, 400 mg 8 hourly with meals.

OR

- Morphine, IM, 0.1 mg/kg 4 hourly as needed, to a maximum of 10 mg.

LoE:IVb[xliv]

6.15 DEHYDRATION/KETOSIS IN LABOUR

O99.2 + (E86)

DESCRIPTION

Subclinical dehydration is often missed in labour.

GENERAL MEASURES

Encourage adequate oral fluid intake.

MEDICINE TREATMENT

Mild dehydration
Give oral fluids.

Moderate/severe dehydration
Administer intravenous fluids, e.g.:

- Sodium chloride 0.9%, IV, 250 mL/hour.

Re-evaluate hydration hourly.

6.16 POSTPARTUM FEVER

O85/O86.0-4/O86.8

DESCRIPTION

During delivery the woman's protective barrier against infections is temporarily reduced and this may lead to infections.
The cause of fever may be a serious complication.
Consider excessive use of misoprostol for PPH (doses >600 mcg) as a possible non-infectious cause of postpartum fever.

GENERAL MEASURES

Prevent deep vein thrombosis.
Complete evacuation of uterine contents.
Hysterectomy may be indicated in severe uterine sepsis.
Attention to breast engorgement.

MEDICINE TREATMENT

Antibiotic treatment, where appropriate, should be guided by the presumed source of infection.

Empiric antibiotic therapy

- Amoxicillin/clavulanic acid, IV, 1.2 g 8 hourly, until patient apyrexial for 24 hours. A

LoE:IVb

Follow with:

- Amoxicillin/clavulanic acid, oral, 875/125 mg 12 hourly. A

REFERRAL

» No clinical response to 48 hours of antibiotic treatment.
» Septic shock.

6.17 POSTPARTUM HAEMORRHAGE

O72.1-3 + (Z51.2)

DESCRIPTION

Blood loss >500 mL after birth of the baby or any blood loss which results in haemodynamic instability (tachycardia and/or hypotension).

GENERAL MEASURES

Bimanual compression of the uterus.
Ensure delivery of placenta is complete.
Check for local causes of bleeding.
Balloon tamponade of the uterine cavity should be considered if the patient is to be transferred to another facility.

MEDICINE TREATMENT

Prevention Z29.2

Active management of the 3rd stage of labour:

- Oxytocin, IM, 10 units.

Note:

» Delay cord clamping and cutting (after 1 minute)
» Deliver the placenta by controlled cord traction.

Treatment

Resuscitate.
Put up two IV lines of crystalloid, one of which should contain oxytocin 20 IU.
Cross match and hold blood for transfusion.
Monitor BP and pulse, and response to uterotonics every 15 minutes.

- Oxytocin, IV, 20 units in 1 L sodium chloride 0.9% at 250 mL/hour.

If uterus remains atonic (palpable above the umbilicus) after the oxytocin infusion has started:

- Ergometrine, IM, 0.5 mg.
  or
  a combination of oxytocin, IM, 5 units and ergometrine, IM, 0.5 mg.
  - Avoid ergometrine in women with hypertension or cardiac disease, except in severe cases where the benefit is considered to outweigh the risk (discuss with a specialist).
  - Repeat ergometrine 0.5 mg IM after 15 minutes if no response.

AND *LoE:Ia*[xlvi]

- Tranexamic acid 1 g, IV, slowly over 10 minutes.
  - Repeat after 30 minutes if there is ongoing vaginal bleeding.

In settings where oxytocin had NOT been administered as prophylaxis at birth:

- Misoprostol, sublingual, or rectal, 600 mcg as a single dose.

LoE:IIb[xlvii]

6.18 THE RHESUS NEGATIVE WOMAN

O36.0 + (Z29.1)

GENERAL MEASURES

Maternal serum antibodies absent

Prevention

Test for maternal serum antibodies at 'booking', 28- and 34-weeks' gestation.
During pregnancy, give prophylactic anti-D immunoglobulin to the mother within 72 hours of a potentially sensitising event.

MEDICINE TREATMENT

After a termination of pregnancy (TOP), miscarriage, ectopic pregnancy or amniocentesis <20 weeks:

LoE:IIIb[xlviii]

- Anti-D immunoglobulin, IM, 50 mcg.

After external cephalic version or potentially sensitizing event ≥20 weeks:

- Anti-D immunoglobulin, IM, 100 mcg.

At birth, determine the Rh status of the cord blood and request a Coomb's test:
Cord blood Rh negative - no treatment.
Cord blood Rh positive, Coomb's negative:

- Anti-D immunoglobulin, IM, 100 mcg.

If a large feto-maternal haemorrhage is suspected:

- Anti-D immunoglobulin, IM, 300 mcg for every 30 mL haemorrhage.
  - Maximum dose: 1 200 mcg.

AND
Do a maternal blood Kleihauer test (consult a specialist).

Rh positive, Coomb's positive:
In these cases, the mother will also have antibodies.
Do not administer anti-D immunoglobulin.

Maternal serum antibodies present.
Consult a specialist.

6.19 URINARY TRACT INFECTION (UTI) IN PREGNANCY

6.19.1 CYSTITIS

O23.1

DESCRIPTION

This condition usually presents with lower abdominal pain, frequency of micturition, and/or dysuria. There are no features of sepsis, e.g., fever. Urine dipstick testing usually shows nitrites, with/without leukocytes; and/or blood.

GENERAL MEASURES

Encourage oral fluid intake.
Midstream urine for microscopy, culture and sensitivity.

MEDICINE TREATMENT

Empiric treatment (symptoms present with nitrites positive **AND** leukocytes positive on dipstick):

- Fosfomycin, oral, 3 g as a single dose — LoE:IIIb[xlix] / LoE:Ib[l]

OR

- Nitrofurantoin, oral, 100 mg, 6 hourly for 5 days.

REFFERAL/CONSULTATION

LoE:IIbli

No response to treatment, or resistant organism on culture.

6.19.2 PYELONEPHRITIS, ACUTE

O23.0

DESCRIPTION

This condition is more serious than cystitis and may result in preterm labour.
Features of pyelonephritis include:

» temperature ≥ 38ºC,
» renal angle tenderness (often bilateral),
» other features of sepsis, i.e., vomiting, tachypnoea, tachycardia, confusion and hypotension.

GENERAL MEASURES

Admit to hospital.
Ensure adequate hydration with intravenous fluids, up to 3 L of sodium chloride 0.9% over 24 hours.
Midstream urine for microscopy, culture and sensitivity.

MEDICINE TREATMENT

Empiric therapy:

- Ceftriaxone, IV, 1 g, daily for 48 hours, or until fever subsides. W

OR

- Gentamicin, IV, 6 mg/kg, daily (ensure normal renal function). A

Switch to oral therapy as soon as the patient is able to take oral fluids:

- Amoxicillin/clavulanic acid, oral, 875/125 mg 12 hourly for 7 days. A

Change antibiotics according to culture and sensitivity results. After treatment, ensure that two urine specimens are negative to confirm eradication.

[i] Department of Health, Republic of South Africa. 2016. Guidelines for Maternity care in South Africa, 4th edition. https://www.knowledgehub.org.za/e-library

[ii] South African Medicines Formulary, 14th Edition. Division of Clinical Pharmacology. University of Cape Town, 2022.

[iii] Ferrous (Iron) supplements, oral - intermittent dosing: National Department of Health: Affordable Medicines, EDP-Primary Health Care level. Medicine Review: Intermittent iron supplementation in pregnancy, 6 November 2017. https://www.knowledgehub.org.za/content/standard-treatment-guidelines-and-essential-medicines-list

Ferrous (Iron) supplements, oral - intermittent dosing: Peña-Rosas JP, De-Regil LM, Gomez Malave H, Flores-Urrutia MC, Dowswell T. Intermittent oral iron supplementation during pregnancy. Cochrane Database Syst Rev. 2015 Oct 19;(10):CD009997. https://www.ncbi.nlm.nih.gov/pubmed/26482110

[iv] Iron (treatment of iron-deficiency anaemia): Reveiz L, Gyte GM, Cuervo LG, Casasbuenas A. Treatments for iron-deficiency anaemia in pregnancy. Cochrane Database Syst Rev. 2011 Oct 5;(10):CD003094. http://www.ncbi.nlm.nih.gov/pubmed/21975735

[v] Therapeutic response to iron (Rise in Hb): Pavord S, Daru J, Prasannan N, Robinson S, Stanworth S, Girling J; BSH Committee. UK guidelines on the management of iron deficiency in pregnancy. Br J Haematol. 2020 Mar;188(6):819-830. https://pubmed.ncbi.nlm.nih.gov/31578718/

Therapeutic response to iron (Rise in Hb): Joint Formulary Committee. British National Formulary. 80. London: BMJ Group and Pharmaceutical Press; 2020.

[vi] Diagnostic criteria for gestational diabetes: NICE. Guideline: Diabetes in pregnancy: management from preconception to the postnatal period, 16 December 2020. https://www.nice.org.uk/guidance/ng3

[vii] Stepwise gestational diabetes approach: NICE. Guideline: Diabetes in pregnancy: management from preconception to the postnatal period, 16 December 2020. https://www.nice.org.uk/guidance/ng3

[viii] Thresholds for diagnosing gestational diabetes: Farrar D, Duley L, Dowswell T, Lawlor DA. Different strategies for diagnosing gestational diabetes to improve maternal and infant health. Cochrane Database Syst Rev. 2017 Aug 23;8:CD007122. https://www.ncbi.nlm.nih.gov/pubmed/28832911

Thresholds for diagnosing gestational diabetes: National Collaborating Centre for Women's and Children's Health (UK). Diabetes in Pregnancy: Management of Diabetes and Its Complications from Preconception to the Postnatal Period. London: National Institute for Health and Care Excellence (UK); 2015 Feb. https://www.nice.org.uk/guidance/ng3/resources/diabetes-in-pregnancy-management-from-preconception-to-the-postnatal-period-51038446021

[ix] Insulin dosing in pregnancy: NICE. Guideline: Diabetes in pregnancy: management from preconception to the postnatal period, 16 December 2020. https://www.nice.org.uk/guidance/ng3

[x] Insulin dosing (pregnancy): Nachum Z, Ben-Shlomo I, Weiner E, Shalev E. Twice daily versus four times daily insulin dose regimens for diabetes in pregnancy: randomised controlled trial. BMJ. 1999 Nov 6;319(7219):1223-7. https://www.ncbi.nlm.nih.gov/pubmed/10550081

[xi] Spironolactone, oral (contra-indicated in pregnancy): South African Medicines Formulary, 14th Edition. Division of Clinical Pharmacology. University of Cape Town, 2022.

[xii] Antihypertensive combination therapy: Hypertension guideline working group, Seedat YK, Rayner BL, Veriava Y. South African hypertension practice guideline 2014. Cardiovasc J Afr. 2014 Nov-Dec;25(6):288-94.http://www.ncbi.nlm.nih.gov/pubmed/25629715

[xiii] Calcium channel blocker (amlodipine/ nifedipine): Abalos E, Duley L, Steyn DW, Gialdini C. Antihypertensive drug therapy for mild to moderate hypertension during pregnancy. Cochrane Database Syst Rev. 2018 Oct 1;10(10):CD002252. https://pubmed.ncbi.nlm.nih.gov/30277556/

Calcium channel blocker (amlodipine/ nifedipine): Magee LA, Brown MA, Hall DR, Gupte S, Hennessy A, Ananth Karumanchi S et al. The Hypertensive Disorders of Pregnancy: The 2021 International Society for the Study of Hypertesion in Pregnancy Classification, Diagnosis & Management Recommendations for International Practice, Pregnancy Hypertension: An International Journal of Women's Cardiovascular Health (2021). https://doi.org/10.1016/j.preghy.2021.09.008

Calcium channel blocker (amlodipine/ nifedipine): Moodley J, Soma-Pillay P, Buchmann E, Pattinson RC. Hypertensive disorders in pregnancy: 2019 National guideline. S Afr Med J. 2019 Sep 13;109(9):12723. https://pubmed.ncbi.nlm.nih.gov/31635598/

[xiv] Nifedipine (dosing interval): Prevost RR, Akl SA, Whybrew WD, Sibai BM. Oral nifedipine pharmacokinetics in pregnancy-induced hypertension. Pharmacotherapy. 1992;12(3):174-7. http://www.ncbi.nlm.nih.gov/pubmed/1951561

Nifedipine (dosing interval): Committee on Obstetric Practice. Committee Opinion No. 623: Emergent therapy for acute-onset, severe hypertension during pregnancy and the postpartum period. Obstet Gynecol. 2015 Feb;125(2):521-5. http://www.ncbi.nlm.nih.gov/pubmed/25611642

Nifedipine (dosing interval): Mol BW, Roberts CT, Thangaratinam S, Magee LA, de Groot CJ, Hofmeyr GJ. Pre-eclampsia. Lancet. 2015 Sep 2. pii: S0140-6736(15)00070-7. http://www.ncbi.nlm.nih.gov/pubmed/26342729

[xv] Labetalol, IV infusion: Raheem IA, Saaid R, Omar SZ, Tan PC. Oral nifedipine versus intravenous labetalol for acute blood pressure control in hypertensive emergencies of pregnancy: a randomised trial. BJOG. 2012 Jan;119(1):78-85. http://www.ncbi.nlm.nih.gov/pubmed/21985500

[xvi] Oxytocin, IM: Department of Health, Republic of South Africa. 2016. Guidelines for Maternity care in South Africa, 4th edition. https://www.knowledgehub.org.za/e-library

[xvii] Aspirin, dose - prevention of preeclampsia: Duley L, Meher S, Hunter KE, Seidler AL, Askie LM. Antiplatelet agents for preventing pre-eclampsia and its complications. Cochrane Database Syst Rev. 2019 Oct 30;2019(10):CD004659. https://pubmed.ncbi.nlm.nih.gov/31684684/

Aspirin, oral - prevention of preeclampsia (safety from 6 weeks' gestation): Hoffman MK, Goudar SS, Kodkany BS, Metgud M, Somannavar M, Okitawutshu J et al; ASPIRIN Study Group. Low-dose aspirin for the prevention of preterm delivery in nulliparous women with a singleton pregnancy (ASPIRIN): a randomised, double-blind, placebo-controlled trial. Lancet. 2020 Jan 25;395(10220):285-293. https://www.ncbi.nlm.nih.gov/pubmed/31982074

Aspirin, oral - prevention of preeclampsia (safety from 6 weeks' gestation): National Department of Health: Affordable Medicines, EDP-Adult Hospital level. Review: Safety of aspirin in pregnancy, February 2020. https://www.knowledgehub.org.za/content/standard-treatment-guidelines-and-essential-medicines-list

[xviii] Calcium: Hofmeyr GJ, Lawrie TA, Atallah ÁN, Torloni MR. Calcium supplementation during pregnancy for preventing hypertensive disorders and related problems. Cochrane Database Syst Rev. 2018 Oct 1;10(10):CD001059. https://pubmed.ncbi.nlm.nih.gov/30277579/

Calcium: WHO. WHO recommendations for prevention and treatment of pre-eclampsia and eclampsia, 2011. http://www.who.int/reproductivehealth/publications/maternal_perinatal_health/9789241548335/en/

[xix] Doppler screening: Magee LA, Brown MA, Hall DR, Gupte S, Hennessy A, Ananth Karumanchi S et al. The Hypertensive Disorders of Pregnancy: The 2021 International Society for the Study of Hypertesion in Pregnancy Classification, Diagnosis & Management Recommendations for International Practice, Pregnancy Hypertension: An International Journal of Women's Cardiovascular Health (2021). https://doi.org/10.1016/j.preghy.2021.09.008

Doppler screening: Alfirevic Z, Stampalija T, Dowswell T. Fetal and umbilical Doppler ultrasound in high-risk pregnancies. Cochrane Database Syst Rev. 2017 Jun 13;6(6):CD007529. https://pubmed.ncbi.nlm.nih.gov/28613398/

Doppler screening: Frusca T, Todros T, Lees C, Bilardo CM; TRUFFLE Investigators. Outcome in early-onset fetal growth restriction is best combining computerized fetal heart rate analysis with ductus venosus Doppler: insights from the Trial of Umbilical and Fetal Flow in Europe. Am J Obstet Gynecol. 2018 Feb;218(2S):S783-S789. https://pubmed.ncbi.nlm.nih.gov/29422211/

[xx] Risk of preterm birth (COVID-19): Chinn J, Sedighim S, Kirby KA, Hohmann S, Hameed AB, Jolley J, Nguyen NT. Characteristics and Outcomes of Women With COVID-19 Giving Birth at US Academic Centers During the COVID-19 Pandemic. JAMA Netw Open. 2021 Aug 2;4(8):e2120456. https://pubmed.ncbi.nlm.nih.gov/34379123/

[xxi] Risk of hospitalisation (Obese COVID-19 pregnant women): Chinn J, Sedighim S, Kirby KA, Hohmann S, Hameed AB, Jolley J, Nguyen NT. Characteristics and Outcomes of Women With COVID-19 Giving Birth at US Academic Centers During the COVID-19 Pandemic. JAMA Netw Open. 2021 Aug 2;4(8):e2120456. https://pubmed.ncbi.nlm.nih.gov/34379123/

[xxii] Corticosteroid therapy (pregnancy): National Department of Health: Affordable Medicines, EDP-NEMLC COVID-19. Rapid review: Corticosteroids for COVID-19: evidence review of the clinical benefit and harm, 24 October 2020. https://www.knowledgehub.org.za/content/standard-treatment-guidelines-and-essential-medicines-list

Corticosteroid therapy (pregnancy): WHO Rapid Evidence Appraisal for COVID-19 Therapies (REACT) Working Group, Sterne JAC, Murthy S, Diaz JV et al. Association Between Administration of Systemic Corticosteroids and Mortality Among Critically Ill Patients With COVID-19: A Meta-analysis. JAMA. 2020 Sep 2;324(13):1–13. https://pubmed.ncbi.nlm.nih.gov/32876694/

[xxiii] Dolutegravir (WOCP & pregnancy): National Department of Health: Affordable Medicines, EDP-PHC/Adult Hospital level. Medicine Review: Dolutegravir in pregnancy, June, 2021. https://www.knowledgehub.org.za/content/standard-treatment-guidelines-and-essential-medicines-list

[xxiv] ART regimens (pregnancy): WHO. Consolidated guidelines on HIV prevention, testing, treatment, service delivery and monitoring: recommendations for a public health approach, July 2021. https://www.who.int/publications/i/item/9789240031593

ART in pregnancy: National Department of Health: National Consolidated Guidelines for the Management of HIV in Adults, Adolescents, Children and Infants and Prevention of Mother-to-Child Transmission, June 2020. https://www.knowledgehub.org.za/elibrary/national-consolidated-guidelines-management-hiv-adults-adolescents-children-and-infants

[xxv] Benzathine benzylpenicillin (late latent syphilis/of unknown duration): Workowski KA, Bolan GA. Workowski KA, Bolan GA; Centers for Disease Control and Prevention. Sexually transmitted diseases treatment guidelines, 2015 [published correction appears in MMWR Recomm Rep. 2015 Aug 28;64(33):924] MMWR Recomm Rep. 2015;64(RR-03):1-137. https://pubmed.ncbi.nlm.nih.gov/26042815/

Benzathine benzylpenicillin (late latent syphilis/of unknown duration): World Health Organization: WHO Guidelines for the treatment of Treponema palladum (syphilis), 2016. https://www.who.int/reproductivehealth/publications/rtis/syphilis-treatment-guidelines/en/

[xxvi] Tenofovir (Pregnant women: HBsAG/ HBeAG positive & HIV negative): National Department of Health: Affordable Medicines, EDP- PHC and Adult Hospital level. Medicine Review: Use of antivirals in the third trimester of pregnancy, in HIV Negative women with chronic active Hepatitis B infection who are HBeAG positive, to prevent vertical transmission of Hepatitis B, May 2024. http://www.health.gov.za/.

[xxvii] Promethazine, oral/parenteral (first-line therapy for hyperemesis gravidarum): The Royal College of Obstetricians and Gynaecologists. The Management of Nausea and Vomiting of Pregnancy and Hyperemesis Gravidarum (Green-top Guideline No. 69), 22 June 2016. https://www.rcog.org.uk/en/guidelines-research-services/guidelines/gtg69/

[xxviii] Metoclopramide, oral/parenteral (second-line therapy for hyperemesis gravidarum): The Royal College of Obstetricians and Gynaecologists. The Management of Nausea and Vomiting of Pregnancy and Hyperemesis Gravidarum (Green-top Guideline No. 69), 22 June 2016. https://www.rcog.org.uk/en/guidelines-research-services/guidelines/gtg69/

[xxix] Ondansetron, parenteral (in pregnancy): Kaplan YC, Richardson JL, Keskin-Arslan E, Erol-Coskun H, Kennedy D. Use of ondansetron during pregnancy and the risk of major congenital malformations: A systematic review and meta-analysis. Reprod Toxicol. 2019;86:1-13. https://pubmed.ncbi.nlm.nih.gov/30849498/

Ondansetron, parenteral (in pregnancy): Huybrechts KF, Hernández-Díaz S, Straub L, et al. Association of Maternal First-Trimester Ondansetron Use With Cardiac Malformations and Oral Clefts in Offspring. JAMA. 2018;320(23):2429-2437. https://pubmed.ncbi.nlm.nih.gov/30561479/

Ondansetron, parenteral (in pregnancy): Huybrechts KF, Hernandez-Diaz S, Straub L, et al. Intravenous Ondansetron in Pregnancy and Risk of Congenital Malformations [published online ahead of print, 2019 Nov 15]. JAMA. 2019;323(4):372-374. https://pubmed.ncbi.nlm.nih.gov/31730152/

[xxx] Indomethacin: Haas DM, Caldwell DM, Kirkpatrick P, McIntosh JJ, Welton NJ. Tocolytic therapy for preterm delivery: systematic review and network meta-analysis. BMJ. 2012 Oct 9;345:e6226. https://pubmed.ncbi.nlm.nih.gov/23048010/

[xxxi] Betamethasone, IM: McGoldrick E, Stewart F, Parker R, Dalziel SR. Antenatal corticosteroids for accelerating fetal lung maturation for women at risk of preterm birth. Cochrane Database Syst Rev. 2020 Dec 25;12(12):CD004454. https://pubmed.ncbi.nlm.nih.gov/33368142/

Betamethasone, IM: FIGO Working Group on Good Clinical Practice in Maternal-Fetal Medicine. Good clinical practice advice: Antenatal corticosteroids for fetal lung maturation. Int J Gynaecol Obstet. 2019 Mar;144(3):352-355. https://pubmed.ncbi.nlm.nih.gov/30710360/

[xxxii] Dexamethasone, IM: McGoldrick E, Stewart F, Parker R, Dalziel SR. Antenatal corticosteroids for accelerating fetal lung maturation for women at risk of preterm birth. Cochrane Database Syst Rev. 2020 Dec 25;12(12):CD004454. https://pubmed.ncbi.nlm.nih.gov/33368142/

Dexamethasone, IM: FIGO Working Group on Good Clinical Practice in Maternal-Fetal Medicine. Good clinical practice advice: Antenatal corticosteroids for fetal lung maturation. Int J Gynaecol Obstet. 2019 Mar;144(3):352-355. https://pubmed.ncbi.nlm.nih.gov/30710360/

[xxxiii] Antibiotic therapy (PROM): Kenyon S, Boulvain M, Neilson JP. Antibiotics for preterm rupture of membranes. Cochrane Database Syst Rev. 2013 Dec 2;(12):CD001058. https://pubmed.ncbi.nlm.nih.gov/24297389/

Antibiotic therapy (PROM): Verani JR, McGee L, Schrag SJ; Division of Bacterial Diseases, National Center for Immunization and Respiratory Diseases, Centers for Disease Control and Prevention (CDC). Prevention of perinatal group B streptococcal disease--revised guidelines from CDC, 2010. MMWR Recomm Rep. 2010 Nov 19;59(RR-10):1-36. https://pubmed.ncbi.nlm.nih.gov/21088663/

Antibiotic therapy (PROM): ACOG. Prelabor Rupture of Membranes: ACOG Practice Bulletin, Number 217. Obstet Gynecol. 2020 Mar;135(3):e80-e97. https://pubmed.ncbi.nlm.nih.gov/32080050/

Antibiotic therapy (PROM): Navathe R, Schoen CN, Heidari P, Bachilova S, Ward A, Tepper J et al. Azithromycin vs erythromycin for the management of preterm premature rupture of membranes. Am J Obstet Gynecol. 2019 Aug;221(2):144.e1-144.e8. https://pubmed.ncbi.nlm.nih.gov/30904320/

[xxxiv] Penicillin allergic - antibiotic therapy (PROM): Kenyon S, Boulvain M, Neilson JP. Antibiotics for preterm rupture of membranes. Cochrane Database Syst Rev. 2013 Dec 2;(12):CD001058. https://pubmed.ncbi.nlm.nih.gov/24297389/

Penicillin allergic - antibiotic therapy (PROM): Verani JR, McGee L, Schrag SJ; Division of Bacterial Diseases, National Center for Immunization and Respiratory Diseases, Centers for Disease Control and Prevention (CDC). Prevention of perinatal group B streptococcal disease--revised guidelines from CDC, 2010. MMWR Recomm Rep. 2010 Nov 19;59(RR-10):1-36. https://pubmed.ncbi.nlm.nih.gov/21088663/

Penicillin allergic - antibiotic therapy (PROM): ACOG. Prelabor Rupture of Membranes: ACOG Practice Bulletin, Number 217. Obstet Gynecol. 2020 Mar;135(3):e80-e97. https://pubmed.ncbi.nlm.nih.gov/32080050/

Penicillin allergic - antibiotic therapy (PROM): Navathe R, Schoen CN, Heidari P, Bachilova S, Ward A, Tepper J et al. Azithromycin vs erythromycin for the management of preterm premature rupture of membranes. Am J Obstet Gynecol. 2019 Aug;221(2):144.e1-144.e8. https://pubmed.ncbi.nlm.nih.gov/30904320/

[xxxv] Prevention of preterm labour: Alfirevic Z, Stampalija T, Medley N. Cervical stitch (cerclage) for preventing preterm birth in singleton pregnancy. Cochrane Database Syst Rev. 2017 Jun 6;6:CD008991. https://www.ncbi.nlm.nih.gov/pubmed/28586127

Prevention of preterm labour: Jarde A, Lutsiv O, Beyene J, McDonald SD. Vaginal progesterone, oral

progesterone, 17-OHPC, cerclage, and pessary for preventing preterm birth in at-risk singleton pregnancies: an updated systematic review and network meta-analysis. BJOG 2019; 126: 556–567. https://www.ncbi.nlm.nih.gov/pubmed/30480871

Prevention of preterm labour: NICE Guidelines: Preterm Labour and Birth, August 2019 https://www.nice.org.uk/guidance/ng25

[xxxvi] Progesterone, PV: Jarde A, Lutsiv O, Beyene J, McDonald SD. Vaginal progesterone, oral progesterone, 17-OHPC, cerclage, and pessary for preventing preterm birth in at-risk singleton pregnancies: an updated systematic review and network meta-analysis. BJOG 2019; 126: 556–567. https://www.ncbi.nlm.nih.gov/pubmed/30480871

Progesterone, PV: National Department of Health: Affordable Medicines, EDP-Adult Hospital level. Medicine Review: Progesterone, vaginal for prevention of preterm labour, October 2019. https://www.knowledgehub.org.za/content/standard-treatment-guidelines-and-essential-medicines-list

[xxxvii] Cerclage: Alfirevic Z, Stampalija T, Medley N. Cervical stitch (cerclage) for preventing preterm birth in singleton pregnancy. Cochrane Database Syst Rev. 2017 Jun 6;6:CD008991. https://www.ncbi.nlm.nih.gov/pubmed/28586127

Cerclage: NICE Guidelines: Preterm Labour and Birth, August 2019 https://www.nice.org.uk/guidance/ng25

[xxxviii] Salbutamol, IV: Neilson JP, West HM, Dowswell T. Betamimetics for inhibiting preterm labour. Cochrane Database Syst Rev. 2014 Feb 5;2:CD004352. http://www.ncbi.nlm.nih.gov/pubmed/24500892

Salbutamol, IV: South African Medicines Formulary, 14th Edition. Division of Clinical Pharmacology. University of Cape Town, 2022.

[xxxix] Extra-amniotic Foley catheter: PLUS prostaglandin protocol: Al-Ibraheemi Z, Brustman L, Bimson BE, Porat N, Rosenn B. Misoprostol With Foley Bulb Compared With Misoprostol Alone for Cervical Ripening: A Randomized Controlled Trial. Obstet Gynecol. 2018 Jan;131(1):23-29. https://www.ncbi.nlm.nih.gov/pubmed/29215514

Extra-amniotic Foley catheter: PLUS prostaglandin protocol: Osoti A, Kibii DK, Tong TMK, Maranga I. Effect of extra-amniotic Foley's catheter and vaginal misoprostol versus vaginal misoprostol alone on cervical ripening and induction of labor in Kenya, a randomized controlled trial. BMC Pregnancy Childbirth. 2018 Jul 12;18(1):300. https://www.ncbi.nlm.nih.gov/pubmed/30001195

Extra-amniotic Foley catheter: PLUS prostaglandin protocol: World Health Organisation. WHO recommendations for induction of labour, Clinical Practice Guideline, 2011. https://pubmed.ncbi.nlm.nih.gov/23586118/

[xl] Dinoprostone: West HM, Jozwiak M, Dodd JM. Methods of term labour induction for women with a previous caesarean Section. Cochrane Database Syst Rev. 2017 Jun 9;6(6):CD009792. https://pubmed.ncbi.nlm.nih.gov/28599068/

Dinoprostone: Andrikopoulou M, Lavery JA, Ananth CV, Vintzileos AM. Cervical ripening agents in the second trimester of pregnancy in women with a scarred uterus: a systematic review and metaanalysis of observational studies. Am J Obstet Gynecol. 2016 Aug;215(2):177-94. https://pubmed.ncbi.nlm.nih.gov/27018469/

Dinoprostone: South African Medicines Formulary, 14th Edition. Division of Clinical Pharmacology. University of Cape Town, 2022.

[xli] Dinoprostone (contraindication): NICE. Guideline: Inducing labour, 4 November 2021. https://www.nice.org.uk/guidance/NG207

Dinoprostone (contraindication): Pfizer: Prandin E2 vaginal gel package insert.

[xlii] Oxytocin, IV (Cervix favourable (Bishop score ≥7): NICE Clinical Guideline: 70 - Induction of labour, 2008. https://www.nice.org.uk/guidance/cg70/evidence/cg70-induction-of-labour-full-guideline2

[xliii] Amniotomy in HIV-infected pregnant women: Peters H, Byrne L, De Ruiter A, Francis K, Harding K, Taylor GP, Tookey PA, Townsend CL. Duration of ruptured membranes and mother-to-child HIV transmission: a prospective population-based surveillance study. BJOG. 2016 May;123(6):975-81. https://www.ncbi.nlm.nih.gov/pubmed/26011825

[xliv] Morphine, IM: South African Medicines Formulary, 14th Edition. Division of Clinical Pharmacology. University of Cape Town, 2022.

[xlv] Morphine, IM: South African Medicines Formulary, 14th Edition. Division of Clinical Pharmacology. University of Cape Town, 2022.

[xlvi] Tranexamic acid, IV: WOMAN Trial Collaborators. Effect of early tranexamic acid administration on mortality, hysterectomy, and other morbidities in women with post-partum haemorrhage (WOMAN): an international, randomised, double-blind, placebo-controlled trial. Lancet 2017; 6736(17)30638-4. https://www.ncbi.nlm.nih.gov/pubmed/28456509

Tranexamic acid, IV: National Department of Health: Affordable Medicines, EDP-Adult Hospital level. Medicine Review: Tranexamic acid, IV, for management of post partum haemmhorhage in pregnant women, 11 October 2017. https://www.knowledgehub.org.za/content/standard-treatment-guidelines-and-essential-medicines-list

[xlvii] Misoprostol: Essential Steps in Managing Obstetric Emergencies (ESMOE), facilitator's guide.

Misoprostol: Hofmeyr GJ, Gülmezoglu AM, Novikova N, Linder V, Ferreira S, Piaggio G. Misoprostol to prevent and treat postpartum haemorrhage: a systematic review and meta-analysis of maternal deaths and dose-related effects. Bull World Health Organ. 2009 Sep;87(9):666-77. http://www.ncbi.nlm.nih.gov/pubmed/19784446

Misoprostol: Department of Health, Republic of South Africa. 2016. Guidelines for Maternity care in South

Africa, 4th edition. https://www.knowledgehub.org.za/e-library

Misoprostol: International Federation Of Gynecology And Obstetrics. Treatment of postpartum hemorrhage with misoprostol. Int J Gynaecol Obstet. 2012 Dec;119(3):215-6. http://www.ncbi.nlm.nih.gov/pubmed/23036964

xlviii Anti-D Immunoglobulin, iM (20 weeks): NICE Clinical Guideline: 156 - Routine antenatal anti-D prophylaxis for women who are rhesus D negative, 2008. https://www.nice.org.uk/guidance/ta156/resources/routine-antenatal-antid-prophylaxis-for-women-who-are-rhesus-d-negative-pdf-82598318102725

xlix Dipsticks (positive nitrites or leukocytes): Mambatta AK, Jayarajan J, Rashme VL, Harini S, Menon S, Kuppusamy J. Reliability of dipstick assay in predicting urinary tract infection. J Family Med Prim Care. 2015 Apr-Jun;4(2):265-8. https://www.ncbi.nlm.nih.gov/pubmed/25949979

Dipsticks (positive nitrites or leukocytes): Demilie T, Beyene G, Melaku S, Tsegaye W. Diagnostic accuracy of rapid urine dipstick test to predict urinary tract infection among pregnant women in Felege Hiwot Referral Hospital, Bahir Dar, North West Ethiopia. BMC Res Notes. 2014 Jul 29;7:481. https://www.ncbi.nlm.nih.gov/pubmed/25073620

l Fosfomycin, oral: Falagas ME, Vouloumanou EK, Togias AG, Karadima M, Kapaskelis AM, Rafailidis PI, Athanasiou S. Fosfomycin versus other antibiotics for the treatment of cystitis: a meta-analysis of randomized controlled trials. J Antimicrob Chemother. 2010 Sep;65(9):1862-77. http://www.ncbi.nlm.nih.gov/pubmed/20587612

Fosfomycin, oral: Lewis DA, Gumede LY, van der Hoven LA, de Gita GN, de Kock EJ, de Lange T, Maseko V, Kekana V, Smuts FP, Perovic O. Antimicrobial susceptibility of organisms causing community-acquired urinary tract infections in Gauteng Province, South Africa. S Afr Med J. 2013 Mar 15;103(6):377-81. http://www.ncbi.nlm.nih.gov/pubmed/23725955

li Nitrofurantoin: Zalmanovici Trestioreanu A, Green H, Paul M, Yaphe J, Leibovici L. Antimicrobial agents for treating uncomplicated urinary tract infection in women. Cochrane Database Syst Rev. 2010 Oct 6;(10):CD007182. https://www.ncbi.nlm.nih.gov/pubmed/20927755

Nitrofurantoin: Lewis DA, Gumede LY, van der Hoven LA, de Gita GN, de Kock EJ, de Lange T, Maseko V, Kekana V, Smuts FP, Perovic O. Antimicrobial susceptibility of organisms causing community-acquired urinary tract infections in Gauteng Province, South Africa. S Afr Med J. 2013 Mar 15;103(6):377-81.http://www.ncbi.nlm.nih.gov/pubmed/23725955

Nitrofurantoin: Nordeng H, Lupattelli A, Romøren M, Koren G. Neonatal outcomes after gestational exposure to nitrofurantoin. Obstet Gynecol. 2013 Feb;121(2 Pt 1):306-13. http://www.ncbi.nlm.nih.gov/pubmed/23344280

CHAPTER 7
NEPHROLOGY/UROLOGICAL DISORDERS

7.1 NEPHROLOGY DISORDERS

CAUTION
Check all medicines for possible dose adjustment based on eGFR

Principles of dosing medication in patients with Chronic Kidney Disease (CKD) and Acute Kidney Injury (AKI)

In the setting of kidney failure, all prescribed medications should be reviewed regularly to ensure that they are safe and at the correct dose for the estimated glomerular filtration rate (eGFR). Currently, the most reliable measure of eGFR is the CKD-EPI in adults and Schwartz equation for children. Nephrotoxic drugs should be avoided in the setting of any kidney dysfunction. Prior to starting any medication, review for previous drug allergies and adverse events. Monitoring of drug toxicity and levels is important where available (e.g. aminoglycosides).

In AKI, the eGFR is not reliable as kidney function changes rapidly. Therefore, it is essential to monitor eGFR and doses of medications regularly. *LoE:IVb* i

Recommendations for medicines that require dose adjustment in renal impairment can be found in the South African Medicine Formulary (SAMF), package insert, and from many online resources e.g.: http://www.globalrph.com/index_renal/

7.1.1 CHRONIC KIDNEY DISEASE (CKD)

N18.1-5/N18.9

DESCRIPTION

Evidence of structural damage (e.g., proteinuria/haematuria) or loss of kidney function (eGFR <60 mL/min/1.73 m^2), present for >3 months.
Markers of kidney damage include:

- proteinuria; (UPCR = urine protein to creatine ratio; UACR = urine albumin to creatine ratio):
  - Severely increased: UPCR >0.05 g/mmol (>0.500g/g); UACR > 30mg/mol (300mg/g).
  - Moderately increased: UPCR 0.015-0.05 g/mmol (0.15-0.5 g/g); UACR 3-30 mg/mmol (30-300 mg/g).

- Normal or mildly increased: UPCR <0.015 g/mmol (<0.15 g/g); UACR <3 mg/mmol (<30 mg/g).

LoE:IVb [ii]

- urine dipstick positive for blood and/or protein (for females with haematuria: exclude current menstrual cycle),
- increased serum creatinine or low eGFR <60 mL/min/1.73 m^2,
- abnormal kidneys on ultrasound, e.g. polycystic, small in size and scarring,
- abnormalities on kidney biopsy,
- electrolyte abnormalities due to tubular disorders,
- history of renal transplant.

eGFR calculator online access:
https://www.kidney.org/apps/professionals/egfr-calculator

Table 7.1: Common causes of CKD

Category	Example
Vascular	Hypertension, renal artery stenosis, vasculitis etc.
Glomerular diseases	Diabetes, autoimmune diseases (e.g. lupus nephritis), chronic systemic infections (e.g. HIV, HBV, syphilis), drugs, neoplasia
Tubulointerstitial diseases	UTI, drug-induced interstitial nephritis (e.g. rifampicin, allopurinol, fluoroquinolones, sulphonamides, beta-lactam antibiotics, proton pump inhibitors, non-steroidal anti-inflammatory drugs)
Structural	Polycystic kidneys, renal masses, obstruction (stones, strictures)
Others	Congenital

Chronic kidney disease can be entirely asymptomatic
until over 75% of kidney function is lost.

TREATMENT AND PREVENTION STRATEGIES ACCORDING TO STAGE OF DISEASE

Adverse outcomes of CKD can often be prevented or delayed through early detection and treatment of risk factors for CKD.
In patients with CKD, the stage of disease should be assigned based on the level of kidney function according to the classification below, irrespective of diagnosis.

Adults with early CKD i.e. stages 0–3 can be managed at primary care level once the cause and plan for care has been established.
All stage 4 and 5 patients require referral/consultation with a specialist. If the patient is a candidate for long-term dialysis, referral to nephrology is advised.

Figure 7.1: Prognosis of CKD by GFR and albuminuria categories: KDIGO 2024

				Persistent albuminuria categories Description and range		
				A1	A2	A3
				Normal to mildly increased	Moderately increased	Severely increased
				ACR* <30 mg/g <3 mg/mmol	ACR* 30–300 mg/g 3–30 mg/mmol	ACR* >300 mg/g >30 mg/mmol
eGFR categories (ml/min per 1.73m^2) - description and range	G1	Normal or high	≥90			
	G2	Mildly decreased	60 –89			
	G3a	Mildly to moderately decreased	45–59			Refer
	G3b	Moderately to severely decreased	30–44		Refer	Refer
	G4	Severely decreased	15–29	Refer	Refer	Refer
	G5	Kidney failure	<15	Refer	Refer	Refer

ACR: albumin to creatinine ratio in urine specimen.

Green: low risk (if no other markers of kidney disease, no CKD); yellow: moderately increased risk; orange: high risk; red: very high risk; A1, A2, A3 = categories of albuminuria; G1, G2, G3a, G3b, G4, G5 = categories of eGFR

LoE:IVb[iii]

GENERAL MEASURES

» Address cardiovascular disease risk factors. See Section 3.1: Ischaemic heart disease and atherosclerosis, prevention.

» Limit total daily salt intake (including salt in food). Consult with dietician as required.

LoE:IVb[iv]

» Avoid nephrotoxic drugs/agents like NSAIDs, aminoglycoside antibiotics and radiocontrast media.

» Regular exercise and target BMI (BMI <25 kg/m^2) according to South African reference ranges.

» Screen for proteinuria.
- If urine dipstick 1+ or greater, repeat on a properly collected midstream urine specimen on another occasion.
- If proteinuria persists, quantify protein with a spot urine protein creatinine ratio. Significant proteinuria = spot urine PCR of >0.15 g/mmol.
- If urine dipstick <1+, measure urine ACR.

» Patients differ in their ability to excrete a salt and water load and therefore fluid balance should be individualised.
» Refer patients to rehabilitation for multidisciplinary care and optimisation of function outcomes e.g., improved muscle strength and cardiovascular fitness, reduced blood pressure, weight management.

LoE:IIIb[v]

MEDICINE TREATMENT

The following interventions may delay progression of kidney disease.

Proteinuria reduction

Ideal targets: UPCR <0.03 g/mmol or UACR <3 mg/mmol.
Most benefit is achieved by reducing UPCR to <0.1 g/mmol or UACR <100 mg/mmol.

- Start treatment with a low dose of ACE-inhibitor and titrate up to the maximum tolerated dose, e.g.
- Enalapril, oral.
  - Start with 5 mg 12 hourly and titrate to 20 mg 12 hourly, if tolerated. LoE:IVb[vi]
  - Monitor creatinine and potassium after 2 weeks if eGFR <60 mL/min/1.73 m^2 and after 4 weeks if eGFR >60 mL/min/1.73 m^2.
  - If creatinine increases by >20% from the baseline, stop ACE-inhibitor and consult a specialist.

LoE:IIIb[vii]

ACE-inhibitor not tolerated due to intractable cough:

- Consider an angiotensin II receptor blocker (ARB), e.g.: (specialist initiated) LoE:IIIb[viii]
- Losartan, oral,
  - Start with 50 mg daily and titrate to 100 mg daily, if tolerated.
  - Replacing ACE-inhibitor with ARB does not preclude the risk of angioedema. LoE:IIa[ix]

CAUTION
ACE-inhibitors and ARBs can cause or exacerbate hyperkalaemia in CKD. Check the serum potassium before starting these medicines and monitor serum potassium on therapy.

Hypertension

Optimise BP control with additional antihypertensive agents. BP control results in a lowering of proteinuria and slower decline in eGFR.
Target BP for patients with hypertension: <140/90 mmHg.
Target BP for patients with hypertension and confirmed CKD and/or diabetes: <130/80 mmHg.
See Section 3.6: Hypertension.

Hyperlipidaemia
If hyperlipidaemia is a co-existent cardiovascular risk factor, manage according to Section 3.1: Ischaemic heart disease and atherosclerosis, prevention.

Diabetes mellitus
In diabetics, optimise control according to Section 8.5: Diabetes mellitus.
In diabetics with kidney disease there is an increased risk of hypoglycaemia.

Insulin is the safer option to control blood glucose in patients with eGFR<60 mL/min/1.73m^2.

Note:
» Insulin requirements will decrease as kidney disease progresses.
» Stop glibenclamide when eGFR <60 mL/min/1.73 m^2 because of an increased risk of hypoglycaemia.
» Reduce metformin dose when eGFR <60 mL/min/1.73 m^2 (maximum dose 500 mg 12 hourly).
» Discontinue metformin when eGFR <30 mL/min/1.73 m^2 because of the risk of lactic acidosis.

LoE:IIIb[x]

Fluid overload and oedema
- Furosemide, oral or IV, 20 to 80 mg daily, as a single or divided doses, initiating at the lowest effective dose and titrating upwards. Dose may be increased to 160 mg daily (IV or oral) in divided doses.
  - First establish an effective dose and ascertain if urination occurs within 1-2 hours of intake. If urination does not occur within 1-2 hours, the dose should be increased further until urination ensues.
  - Diuretic action starts within 60 minutes of dose, hence divided doses should be given in the morning and afternoon, e.g. 8 AM and 2 PM.

LoE:IVb[xi]

When fluid overloaded and eGFR <60 mL/min/1.73 m^2, start:
- Furosemide, oral or IV, 40 mg in divided doses (e.g., 8 AM and 2 PM).
  - Titrate to a maximum of 500 mg in divided doses (e.g., 8 AM and 2 PM).
  - Furosemide is ineffective when patients are on dialysis and anuric.

Hypocalcaemia and hyperphosphatemia
The aim is to lower phosphate levels and maintain normal calcium levels to ensure calcium-phosphate product (i.e. Ca x PO_4) <4.4 mmol^2/L^2, to prevent calcium deposition in vessels and tissue which aggravates vascular disease.

Restrict dietary phosphate intake. (Dietitian consultation.)
https://unckidneycenter.org/kidneyhealthlibrary/nutrition-and-kidney-disease/

Patients with CKD stage 3–5, not on dialysis:
Hyperphosphataemia and/or hypocalcaemia:
- Calcium (elemental), oral, 500 mg 8 hourly with meals if calcium-phosphate product <4.4 mmol^2/L^2.

- Increase to approximately 1 g 8 hourly with meals if hyperphosphatemia persists.

- Aluminium hydroxide 300mg/5ml, oral, 10 mL 8 hourly with meals if calcium-phosphate product >4.4 $mmol^2/L^2$, for two weeks only, then switch to calcium carbonate.

LoE:IVb[xii]

Hypocalcaemia and low or normal serum phosphate:

- Calcium (elemental), oral (calcium carbonate), 500 mg 8 hourly two hours after meals, increase to approximately 1 g 8 hourly between meals.

In patients with CKD stage 5 who are not candidates for kidney replacement therapy, the benefits of phosphate binding are unclear, and regular PTH (parathyroid hormone) monitoring is not necessary.

Patients considered suitable candidates for kidney replacement therapy:
Monitor Ca^{++}, PO_4 and PTH levels, as per Figure 7.1

For hyperphosphataemia uncontrolled on calcium carbonate:

- Aluminium hydroxide BP (300 mg/5 mL), oral, 10 mL 8 hourly. (Specialist initiated.)
  - To prevent dementia associated with chronic aluminium toxicity, do not use for longer than 3 months.

For hyperparathyroidism, initiate when PTH levels >2 times upper limit of normal range: (Specialist initiated)
(N25.8)

- Calciferol, oral, 50 000 IU once weekly. *LoE:IIIb*[xiii]

OR

- Calcitriol, oral, 0.25–4 mcg daily.

Anaemia associated with CKD in patients on dialysis programmes
N18.3-5†/N18.9† + (D63.8*/Z49.1-2)

Patients on chronic haemodialysis or peritoneal dialysis are often anaemic due to iron deficiency and deficiency of erythropoietin (EPO).
Simultaneous administration of iron and EPO is recommended, as **EPO should be administered in a patient with normal iron stores.** Adequate iron stores are required to assist with red blood cell production immediately after EPO administration (see Section 2.1.1: Anaemia, iron deficiency).

LoE:IIa[xiv]

- Iron, elemental, oral. See Section 2.1.1: Anaemia, iron deficiency, if no response, consider parenteral iron.

AND

- Erythropoietin Stimulating Agents (ESAs), e.g.:
- Erythropoietin alpha or beta, 40–50 IU/kg/dose, IV/SC 2–3 times weekly and assessed at 4 weekly intervals.

- Administer IV dose over 1–5 minutes.
- If necessary, dose may be increased by 25 IU/kg.
- Note: There is an increased risk of cardiovascular events with haemoglobin levels >12 g/dL.

LoE:IIa[xv]

Definitive treatment, e.g. transplantation, usually improves anaemia. It is important to identify factors likely to aggravate anaemia, e.g. iron deficiency, infection, and vitamin B_{12} and folate deficiency.

Acidosis and hyperkalaemia
Specialist consultation for possible kidney replacement therapy.

Check all medicines for possible dose adjustments.
http://www.globalrph.com/index_renal.htm

CONSULT WITH A SPECIALIST AT THE LOCAL REFERRAL CENTRE IF:

» Unknown cause of kidney failure.
» Rapid deterioration in kidney function.
» Resistant hypertension despite appropriate medication and adherence.
» All patients with persistent proteinuria: on urine dipstick ≥ 1+ or proteinuria >1 g/24 hours (UPCR >0.1 g/mmol).
» Patients with nephrotic-range proteinuria (UPCR >0.35 g/mmol) or nephrotic syndrome should be referred for possible kidney biopsy.

REFERRAL

» All ESKD patients who may qualify for long term dialysis programs. See Section 7.1.5: Kidney replacement therapy.
» CKD stage 3 and above (see Figure 7.1: Prognosis of CKD by GFR and albuminuria categories).

7.1.2 GLOMERULAR DISEASE AND NEPHRITIC SYNDROME

N04.9/N05.9

DESCRIPTION

Acute glomerulonephritis presents with one or more of the following: haematuria, proteinuria, an acute decrease in eGFR, fluid retention, or hypertension.

GENERAL MEASURES

» Give oxygen, and place patient in semi-Fowler's position if patient has respiratory distress/pulmonary oedema.
» Early consultation with a specialist.
» Regulate fluid and electrolyte balance. Monitor weight closely.

» Dietary modification if severe kidney dysfunction, e.g. restrict salt, protein, potassium and phosphate intake.
» Avoid potential nephrotoxins: e.g. NSAIDs, aminoglycosides.

MEDICINE TREATMENT

Fluid overload

- Furosemide, as a slow IV bolus, 80 mg.
  - Avoid unnecessary intravenous fluids.

If hypertension present: I12.0/I12.9
Diastolic BP >100 mmHg or systolic BP >150 mmHg:

- Amlodipine, oral, 5 mg as a single dose.

AND

- Furosemide, oral, 40–80 mg (if eGFR <30 mL/min/1.73m^2).

OR

- Hydrochlorothiazide, oral, 25 mg (if eGFR ≥30 mL/min/1.73m^2).

Check all medicines for possible dose adjustments.
http://www.globalrph.com/index_renal.htm

CONSULTATION/REFERRAL

The management of glomerular disease is individualised, and management of all patients should be discussed with a specialist.

7.1.3 NEPHROTIC SYNDROME

N04.9

DESCRIPTION

Glomerular disease is characterised by:
» Nephrotic-range proteinuria, i.e.: UPCR >0.35 g/mmol
and *LoE:IVb* [xvi]
- oedema,
- hypoalbuminaemia, and
- hyperlipidaemia.

The cause cannot be determined accurately without a kidney biopsy. With the exception of diabetic nephropathy, all other causes of nephrotic syndrome require specialist consultation.

GENERAL MEASURES

Regulate salt and fluid intake.
Weigh regularly to assess fluid retention.
Check for postural hypotension to identify excessive diuresis.
Evaluate proteinuria with PCR:
» initially – weekly,
» when discharged – monthly, until stable.

Monitor potassium frequently for patients on ACE-inhibitors and/or diuretics.

MEDICINE TREATMENT
Management should be guided by a specialist.

CONSULTATION/REFERRAL
All patients.

7.1.4 ACUTE KIDNEY INJURY
N17.9

DESCRIPTION
Kidney injury may be due to a combination of factors.
Acute kidney injury (AKI) is defined as any of the following:
» Increase in serum creatinine by ≥26.5 µmol/L within 48 hours; or
» Increase in serum creatinine to ≥1.5 times baseline, which is known or presumed to have occurred within the prior 7 days; or
» Urine volume <0.5 mL/kg/hour for 6 hours.

GENERAL MEASURES
A detailed history and good clinical examination are necessary to identify potentially reversible causes. Ensure volume status, perfusion and oxygenation. Monitor serum creatinine, potassium and urine output.
If radiocontrast diagnostic procedures are required, see Section 22.1: Diagnostic contrast agents and related substances.
Avoid any nephrotoxic medicines e.g. NSAIDs, aminoglycosides. Check all medicines for possible dose adjustments.

MEDICINE TREATMENT
Fluid overload
In patients with fluid overload where dialysis is not immediately available, a short trial of high dose furosemide in consultation with a specialist may be appropriate.

Acute dialysis
Discuss all cases with the referral centre.
Common indications for acute dialysis include:
» Pulmonary oedema refractory to medical therapy.
» Severe metabolic acidosis (pH < 7.15) refractory to medical therapy
» Severe hyperkalaemia (>7 mmol/L) refractory to medical therapy
» Uraemic complications, e.g. pericarditis, encephalopathy and bleeding.
» Medication overdose if due to dialysable toxin. See Section 19: Exposure to poisonous substances.

LoE:IVb[xvii]

Note: HIV infection is not a contra-indication for acute dialysis.

Both haemodialysis and peritoneal dialysis are acceptable modalities of therapy in the acute setting.

Peritoneal dialysis effluent is potentially infectious when used in patients with HIV and viral hepatitis.

Hyperkalaemia

Serum K^+ >6.0 mmol/L. LoE:IVb[xviii]

Emergency measures

Calcium gluconate 10%, slow IV bolus, 10 mL over 10 minutes. Subsequent doses should be considered if ECG changes persist after 5 minutes or recur.

AND

- Dextrose 50%, IV bolus, 100 mL followed by soluble insulin, 10 units administered as a push over 5 minutes.
  - Monitor blood glucose levels hourly up to 6 hours post-insulin administration.

AND

- Salbutamol nebulisation, 10-20 mg. LoE:IIb[xix]
  - Dilute salbutamol 0.5% (5 mg/mL), solution, 1 mL (5 mg) salbutamol 0.5% solution made up to 4 mL with sodium chloride 0.9%.

These are short-term measures - patients should be dialysed or if this is not feasible:

- Sodium polystyrene sulfonate, oral, 15 g with 15 mL lactulose, 6 hourly.

OR

- Sodium polystyrene sulfonate, rectal, 30–60 g as an enema.
  - After 8 hours, wash out with phosphate enema.

Note: Rectal administration is less effective.

Glycaemic control

Close glycaemic control can reduce the incidence and severity of AKI.
See Section 8.5: Diabetes mellitus.

Some patients do not recover kidney function and should be treated as CKD (See Section 7.1.1: Chronic kidney disease).

7.1.5 KIDNEY REPLACEMENT THERAPY

Z99.2

Refer to the current National Department of Health Guidelines for renal dialysis.

PATIENT SELECTION

The final decision for selection of patients for kidney replacement therapy should be made by a multidisciplinary team using standardised selection criteria.

The ideal patient for kidney replacement therapy has uncomplicated CKD stage 5 (ESKD) and **must be a suitable candidate for kidney transplantation**.

Individual nephrology units have their own eligibility criteria, and these may include:

» presence of systemic illnesses,
» age,
» BMI, and
» psychosocial factors.

Obtain these guidelines from the referral centre.

7.2 MAJOR ELECTROLYTE ABNORMALITIES

Guidance provided on potassium and sodium electrolyte imbalances.

7.2.1 HYPERKALAEMIA

E87.5

See Section 7.1.4: Acute kidney injury.

7.2.2 HYPOKALAEMIA

E87.6

DESCRIPTION

A serum potassium level <3.5 mmol/L.

Mild to moderate symptoms: muscle weakness (respiratory, and GIT muscles) and cramps.

Severe symptoms: rhabdomyolysis, paralysis, dysrhythmias, diaphragmatic weakness.

Signs of hypokalaemia: cardiac arrhythmias and/or ECG abnormalities (Prolonged QT interval, bradycardia).

Identify and treat/remove the cause: It is usually due to gastro-intestinal losses (diarrhoea) or kidney losses (diuretic therapy, hyperaldosteronism, vomiting).

MEDICINE TREATMENT

For chronic asymptomatic hypokalaemia, look for and manage the cause:

- Potassium chloride, oral, 600 mg, 1–2 tablets 8 hourly.
  - Each 600 mg potassium chloride tablet contains 8 mmol of potassium chloride.
  - Titrate according to response to therapy.

*LoE:IVb*XX

- Maximum daily dose: 6 g (i.e.10 tablets per day in divided doses).
- Review potassium levels after 4 weeks.

OR

- Potassium chloride solution (1g/5ml) 10-30 mL daily in divided doses PO up to 6 g. (See Appendix IV: Extemporaneous preparations for the preparation formula for adults.)

Note: Routine supplementation with potassium chloride in patients who are on diuretics is usually inappropriate. Co-administration of ACE-inhibitors and/or spironolactone counteracts the hypokalaemia from furosemide or thiazides. In patients that develop hypokalaemia while using potassium-sparing diuretics or ACE- inhibitors/ARBs, consider underlying primary hyperaldosteronism.

For mild to moderate hypokalaemia in a non-vomiting patient (potassium level usually 3–3.4 mmol/L):

- Potassium chloride, oral, 1 200 mg (2 tablets) 8 hourly.
  - Each 600 mg potassium chloride tablet contains 8 mmol of potassium chloride.
  - Titrate according to response to therapy.
  - Maximum daily dose: 6 g (i.e.10 tablets per day in divided doses).
  - Continue treatment until the serum potassium concentration is persistently above 3.5 mmol/L and symptoms or signs have resolved.

OR

- Potassium chloride solution (1 g/5ml), oral, 10-30 mL daily in divided doses up to 6 g. (See Appendix IV: Extemporaneous preparations for the preparation formula in adults.)

LoE:IVb[xxi]

For severe, symptomatic hypokalaemia:

- Potassium chloride, IV by peripheral line, 40 mmol in 1 L of 0.9% or 0.45% sodium chloride, mixed thoroughly.
  - Administer over 3 hours, or up to a maximum rate of 20 mmol per hour. Beware of volume overload. (See Appendix II, for individual dosing and monitoring for response and toxicity.)
  - Repeat as required, monitoring potassium serum levels after each replacement dose.
  - One potassium chloride 15% 10 mL ampoule contains 20 mmol potassium.
  - Maximum allowed daily dose of K^+ is 3 mmol/kg/day (or 400 mmol/day).

LoE:IIIb[xxii]

CAUTION
Potassium chloride ampoules must always be diluted before infusion.

Reduce the rate of intravenous potassium repletion or change to oral therapy once the hypokalaemia is no longer severe. Continue treatment until the serum potassium concentration is persistently above 3.5 mmol/L and symptoms or signs have resolved.

Online calculator for calculating potassium deficit:
http://www.medicinehack.com/2011/07/hypokalemia-potassium-replacement.html

If not responding to therapy, check for hypomagnesaemia as low serum magnesium may potentiate potassium loss.

7.2.3 HYPERNATRAEMIA

E87.0

DESCRIPTION

A serum sodium level >145 mmol/L.

- » Mild to moderate symptoms: Lethargy, weakness, irritability
- » Severe symptoms: Convulsions, coma

In patients who develop hypernatraemia outside of the hospital, it is usually due to water losses (decreased thirst sensation or inability to drink water, e.g. (delirium/reduced consciousness), gastro-intestinal losses (diarrhoea) or renal losses (diabetes insipidus)).

In hospitalised, critically ill patients it is usually the result of sodium gain (administration of too much sodium-containing intravenous solutions).

GENERAL MEASURES

Treat the cause.

Calculate the water deficit:

1. Calculate Total body water = correction factor X weight (kg).
   Correction factor is 0.6 for men, 0.5 for women and elderly men, and 0.45 for elderly women.

2. Calculate water deficit:

$$Water\ deficit = Total\ body\ water \times (1 - \frac{140}{Na^{+}\ concentration})$$

See online calculator:
https://www.msdmanuals.com/professional/multimedia/clinical-calculator/water-deficit-in-hypernatremia

MEDICINE TREATMENT

Correction fluid:

- Oral fluids or via NGT.

If unable to give fluids orally:

- Dextrose 5%, IV infusion.
  - Monitor for hyperglycaemia. Rate of correction of hypernatraemia should be slower than 10 mmol/L over 24 hours to prevent cerebral oedema and rarely, osmotic demyelination syndrome.

Ongoing obligatory water loss through skin and stool (estimated at 30 mL/hour) must also be replaced: LoE:IVb[xxiii]

1. Calculate desired water replacement in the first 24 hours:

$$Water\ deficit \times 10\ mmol/L \div (Serum\ [Na^+] - 140)$$

2. Calculate hourly infusion rate =
   Desired water replacement in the first day ÷ 24 hours + 30 mL/hour.

7.2.4 HYPONATRAEMIA

E87.1

DESCRIPTION

A serum sodium level <135 mmol/L.

Mild to moderate symptoms:	Headache, nausea, vomiting, fatigue, gait disturbances, and confusion.
Severe symptoms:	Seizures, obtundation, coma, and respiratory arrest.

Acute hyponatraemia develops within hours due to self-inflicted water intoxication.

CAUTION

Rapid correction of chronic hyponatraemia may lead to osmotic demyelination syndrome, which is often irreversible and fatal. Sodium should be frequently monitored, and increases should be <8 mmol/L per day.

LoE:IVb[xxiv]

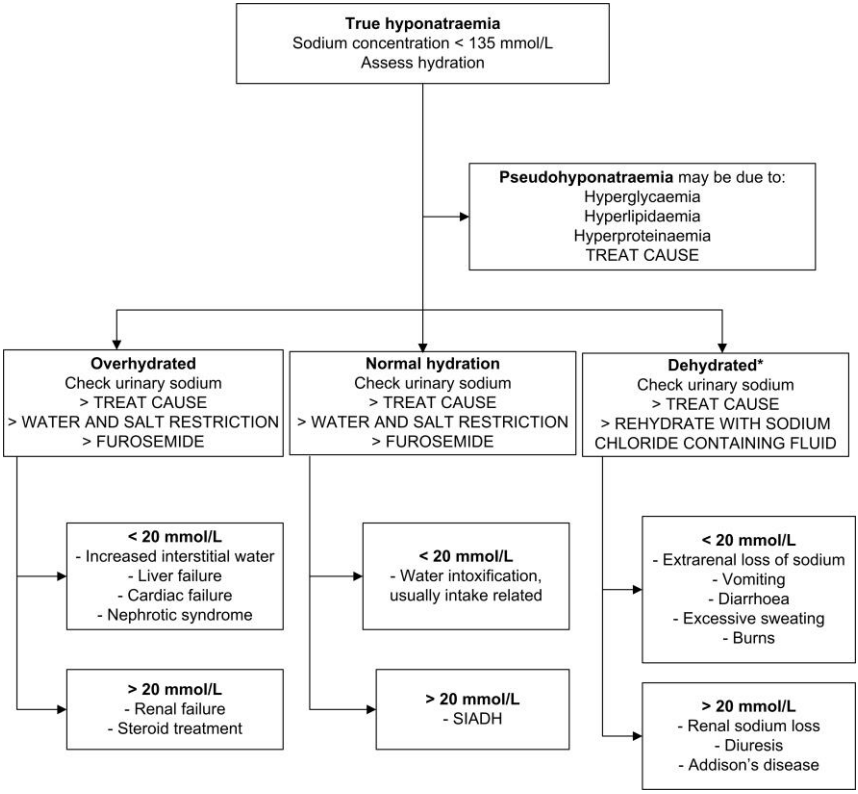


Figure 7.2: Approach to hyponatraemia

LoE:IVb[xxv]

MEDICINE TREATMENT

In the presence of fluid overload:

- Furosemide, oral, 40 mg twice a day in divided doses.
  - Increase dose to control signs of fluid overload and to improve hyponatraemia. *LoE:IVb*[xxvi]

In the absence of fluid overload:

Consult with a specialist before administering sodium chloride, IV infusion.

- Sodium chloride, IV infusion (see Table 7.2 below).

CAUTION

Hypertonic sodium chloride should be reserved for severe acute hyponatraemia (sodium level <120 mmol/L with severe symptoms) and exceptional circumstances. In general, each increase in TBW of 1 mmol will raise the serum sodium concentration by 1 mmol/L.

One litre of NaCl infusate	Total Na (mmol/l)	Indication	Fluid	Aim
5% NaCl Expect an increase of 2-3 mmol/L for every 60 mL	855	» Sodium level <120 mmol/L **and** » Severe symptoms (see above) **or** » Acute hyponatraemia due to water intoxication	• Hypertonic sodium chloride, 5%, 60 mL as an IV bolus over 15 min • If symptoms persist/ worsens or sodium is not improving, consult a specialist	» Symptom relief » Correct hypona-traemia: – 4-6 mmol/L immediately **AND** – Maximum 8 mmol/L in 1st 24 hrs
5% NaCl Expect an increase of 2-3 mmol/L for every 60 mL	855	» Sodium level <120 mmol/L with mild to moderate symptoms **or** » Chronic hyponatraemia	• Hypertonic sodium chloride, 5%, 30 mL as an IV bolus over 15 min	» Symptomatic relief. » Correct hypona-traemia: – Maximum 8 mmol/L in 1st 24 hrs
0.9% NaCl	154	» Sodium level >120 mmol/L » Dehydrated. » Asymptomatic or mild symptoms	• Sodium chloride, 0.9%, IV infusion, 1L 8 hourly	» Rehydration

Table 7.2: Management of hyponatraemia with sodium chloride.

LoE:IVb[xxvii]

To calculate the infusion rate, consult a specialist.
https://reference.medscape.com/calculator/643/sodium-correction-rate-for-hyponatremia

7.3 UROLOGICAL DISORDERS

Disorders of the genitourinary system.

7.3.1 HAEMATURIA

R31/B65.0-3/B65.8-9

DESCRIPTION

Bleeding from the urinary tract, which can be from the kidneys, collecting system, bladder, prostate and urethra.

LoE:IVb[xxviii]

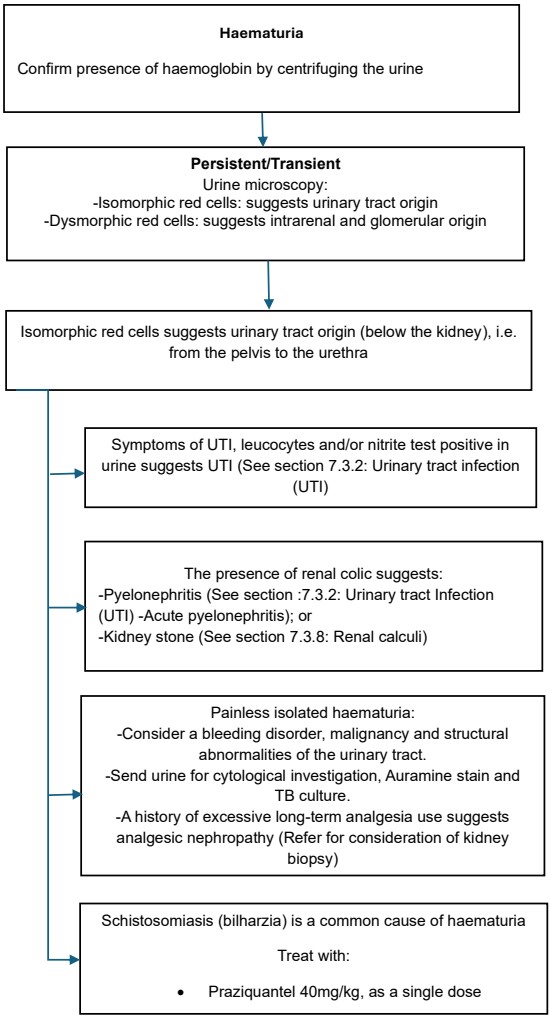


Figure 7.3: Approach to haematuria

REFERRAL

Suspected glomerular disease.

7.3.2 URINARY TRACT INFECTION (UTI)

N10/N30.9/N39.0/O23.4

DESCRIPTION

UTIs include cystitis (infection of the bladder/lower urinary tract) and pyelonephritis (infection of the kidney/upper urinary tract). Pyelonephritis develops when pathogens ascend to the kidneys via the ureters. Uncomplicated UTIs involve either the lower urinary tract (bladder) and/or the upper urinary tract (kidney) in non-pregnant, pre-menopausal woman with no known relevant anatomical and/or functional abnormalities within the urinary tract or any comorbidities. UTIs in other groups of patients are complicated by definition.

Features of upper UTI include:
» flank pain/tenderness,
» temperature >38˚C,
» other features of sepsis, i.e. tachypnoea, tachycardia, confusion and hypotension, or
» nausea and vomiting.

In complicated, recurrent or upper UTIs, mid-stream urine should be sent for microscopy, culture and sensitivity.

MEDICINE TREATMENT

Women with recurrent UTIs should be advised to:
» void bladder after intercourse and before retiring at night,
» not postpone voiding when urge to micturate occurs,
» change from use of diaphragm to an alternative type of contraception.

Empirical treatment is indicated only if:
» positive leucocytes **and** nitrites on urine test strips on freshly passed urine, or
» leucocytes or nitrites with symptoms of UTI, or
» systemic signs and symptoms indicating an upper UTI and/or urosepsis.

Note: Alkalinising agents are not recommended, as many antibiotics require a lower urinary pH.

Uncomplicated community acquired cystitis: N30.9

- Fosfomycin, oral, 3 g as a single dose. W — *LoE:IIb*[xxix]

OR

- Gentamicin, IM, 5 mg/kg as a single dose. A
  - **Note:** Gentamicin should not be used in renal impairment or pregnancy (see Appendix II for guidance on prescribing). *LoE:IIb*[xxx]

  Therapeutic drug monitoring is not required.

OR

- Nitrofurantoin, oral, 100 mg 6 hourly for 5 days. A

LoE:IIb[xxxi]

Complicated community acquired cystitis (Non-pregnant women) N30.9

- Ciprofloxacin, oral, 500 mg 12 hourly for 7 days. W

LoE:IIIb[xxxii]

CAUTION

Concomitant use of fluoroquinolones with ACE-inhibitor/angiotensin receptor blocker is contraindicated in moderate to severe renal impairment (eGFR ≤ 30 ml/min/1.73m^2) and in the elderly. Assess renal function before initiating treatment and monitor during treatment.

Evidence suggests a risk of developing acute kidney injury with concomitant use of fluoroquinolones and renin-angiotensin receptor blockers.

LoE:IIIb[xxxiii]

For pregnant women: O23.4

LoE:Ib[xxxiv]

- Fosfomycin, oral, 3 g as a single dose. W

OR

- Nitrofurantoin, oral, 100 mg 6 hourly for 5 days. A

LoE:IIb[xxxv]

Acute pyelonephritis N10

Admit all patients with vomiting, sepsis, diabetes or impaired/worsened renal function (eGFR <60 mL/min/1.73m^2).

Ensure adequate hydration with intravenous fluids.

If there is a poor response, perform an ultrasound on all hospitalised patients urgently as in-patients.

Adjust antibiotic according to sensitivity.

Duration of antibiotic therapy in uncomplicated pyelonephritis:

» Fluoroquinolones: 7 days

» Other antibiotics: 14 days.

Longer courses of therapy, 2–3 weeks, should be given for complicated pyelonephritis.

Patients who have features of severe sepsis or who are vomiting, initiate IV therapy and switch to oral therapy as soon as clinical condition improves:

If normal renal function:

- Gentamicin, IV, 6 mg/kg daily. A (See Appendix II for guidance on prescribing and monitoring.)

Switch to oral therapy as soon as the patient is able to take oral fluids, according to microscopy culture and sensitivity results:

- Ciprofloxacin, oral, 500 mg 12 hourly for 7–10 days. W

If impaired renal function:

- Ceftriaxone, IV, 1 g daily. W

Switch to oral therapy as soon as the patient is able to take oral fluids, according to microscopy culture and sensitivity results:

- Ciprofloxacin, oral, 500 mg 12 hourly for 7 days. W
  - If severe renal impairment (eGFR <10 mL/min/1.73m^2): 50% of normal dose.

REFFERAL/CONSULTATION

Urgent

» Acute pyelonephritis in pregnant women.
» Acute pyelonephritis with:
  - vomiting
  - sepsis
  - diabetes mellitus
  - urinary tract obstruction on ultrasound

Non-urgent

» Failure to improve within 72 hours.
» Women beyond reproductive age.
» >3 uncomplicated UTIs within a one-year period.
» >1 complicated UTI within a one-year period.

7.3.3 RECURRENT UTI

N10.0/N30.9/N39.0

DESCRIPTION

Recurrences of uncomplicated and/or complicated UTIs, with a frequency of at least three UTIs/year or two UTIs in the last six months.
Send urine for microscopy, culture and sensitivity as treatment is determined by the results. *LoE:IVb*[xxxvi]

GENERAL MEASURES

Women should void soon after intercourse.
Identify and treat hormone-deficient atrophic vulvo-vaginitis in the elderly.

MEDICINE TREATMENT

Prophylaxis (Z29.9)

To reduce risk of recurrence in patients with >3 infections/year requires continuous prophylaxis for 6 months:

- Cotrimoxazole 80/400 mg, oral, 1 tablet at night. A

Treatment

Treat according to microscopy, culture and sensitivity.

REFERRAL/CONSULTATION

» Failure to respond to prophylactic treatment.
» Uncertain diagnosis.
» Recurrent infections where no facilities exist for adequate culture of urine.
» All complicated recurrent UTIs.
» STI pathogens.

7.3.4 PROSTATITIS

N41.1/N41.9 + (N34.2)

DESCRIPTION

Clinical features include:
» pyrexia,
» acute pain in the pelvis and perineum,
» dysuria and frequency,
» urinary retention or difficulty, and
» acutely tender prostate on rectal examination.

Chronic non-bacterial prostatitis

This is a diagnosis of exclusion, i.e. failure to respond to antibiotics. It is associated with perineal, suprapubic, penile and testicular pain.

MEDICINE TREATMENT

Acute bacterial prostatitis

<u>If there are features of associated urethritis (STI regimen):</u>

- Ceftriaxone, IM, 250 mg as a single dose. W

LoE:IIIb[xxxvii]

AND

- Azithromycin, oral, 1 g as a single dose. W

LoE:Ia[xxxviii]

<u>If there are **no** features of associated urethritis:</u>

- Ciprofloxacin, oral, 500 mg 12 hourly for 14 days. W

LoE:IVb

<u>Chronic/relapse/persistent infection:</u> N41.1

- Ciprofloxacin, oral, 500 mg 12 hourly for 28 days. W

LoE:IVb

REFERRAL

To urologist if:
» No response to treatment.
» Urinary retention present.
» Chronic/relapsing prostatitis.

7.3.5 BENIGN PROSTATIC HYPERPLASIA

N40

DESCRIPTION

Benign prostatic hyperplasia is a noncancerous (benign) growth of the prostate gland. It usually occurs in men over 50 years of age.
May be associated with both obstructive (weak, intermittent stream and urinary hesitancy) and irritative (frequency, nocturia and urgency) voiding symptoms.
Digital rectal examination reveals a uniform enlargement of the prostate.
Urinary retention with a distended bladder may be present in the absence of severe symptoms, therefore it is important to palpate for an enlarged bladder during examination.

GENERAL MEASURES

Consult with a urologist.
Annual follow-up.
For patients presenting with urinary retention, insert a urethral catheter.
Stop medication that may aggravate urinary retention e.g. anticholinergics.

MEDICINE TREATMENT

- Alpha blocker, e.g.:
- Doxazosin, oral, 4 mg daily. *LoE:Ia*[xxxix]
  - Initial dose: 1 mg daily.
  - Titrate dose by 1 mg every 2 weeks to clinical effect.
  - Usual maintenance dose: 4 mg daily.

7.3.6 OVERACTIVE BLADDER

N32.8

DESCRIPTION

A clinical syndrome consisting of urinary frequency (day and night time) and urgency, with or without urgency incontinence,

GENERAL MEASURES

Urine dipstick to exclude an UTI.
Health education.
Avoid caffeine containing, alcoholic and carbonated beverages.
Pelvic floor muscle training: three sets of 8-12 contractions sustained for 8-10 seconds each, performed three times a day. Patients should continue for at least 15-20 weeks.

MEDICINE TREATMENT

For detrusor hyperactivity:

- Oxybutynin, oral, 2.5–5 mg 8 hourly. (Specialist initiated.)

LoE:IVb[xi]

REFERRAL
» For confirmation of diagnosis.
» Complications.
» Not responding to medical therapy.

7.3.7 ERECTILE DYSFUNCTION
F52.2/N48.4 + (E29.1)

DESCRIPTION
The inability to attain and maintain an erect penis with sufficient rigidity for sexual intercourse.
Many cases are psychogenic.
Organic causes include neurogenic, vasculogenic or endocrinological disorders; many systemic diseases; pelvic trauma/surgery; and certain medicines.

GENERAL MEASURES
Thorough medical and psychosexual history.
Examination should exclude gynaecomastia, testicular atrophy or penile abnormalities.
Review all medicines and, if possible, withdraw medicines that may be associated with erectile dysfunction.
Identify and treat cardiovascular risk factors e.g. obesity, hypertension, and dyslipidaemia.
Advise on lifestyle modification e.g. cessation of smoking and excessive alcohol use, physical activity, and weight loss.

MEDICINE TREATMENT
Treat the underlying condition.

In patients with proven testosterone deficiency: (E29.1)
- Testosterone. Specialist initiated.

See Section 8.3: Androgen deficiency.

REFERRAL
To a urologist or appropriate specialist if surgical intervention is needed, e.g. penile prostheses, vascular surgery and pelvic fractures.

7.3.8 RENAL CALCULI

N20.0-2/N20.9/N21.0/N21.8/N21.9

DESCRIPTION

A kidney stone or calculus which has formed in the renal tract, i.e. pelvis, ureters or bladder, as a result of urine which is supersaturated with a stone-forming salt.

Clinical features of obstructing urinary stones may include:

» sudden onset of acute colic, localized to the flank, causing the patient to move constantly,
» nausea and vomiting,
» referred pain to the scrotum or labium as the stone moves down the ureter.

Urinalysis usually reveals microscopic or macroscopic haematuria.

Stones may be passed spontaneously, or after medical or invasive treatment. If available, collect the stones and send to the laboratory for analysis.

GENERAL MEASURES

Acute stage:
Oral fluids administered liberally.
Intravenous fluids to ensure adequate hydration and urine flow.

To prevent recurrence:
Avoid dehydration.
If recurrences occur, consult a specialist.

MEDICINE TREATMENT

Analgesia for renal colic:

- NSAID, oral: e.g. *LoE:IIb[xii]*
- Ibuprofen, oral, 400 mg 8 hourly with meals.

Note: Avoid NSAIDs if renal impairment is present or suspected.

If patient is vomiting:

- Diclofenac, IM, 75 mg as a single dose**.** *LoE:IVb*

AND/OR

- Tramadol, oral, 50 to 100 mg, 6 hourly as a starting dose. (Doctor prescribed.)
  - May be increased to a maximum daily dose of 400 mg. *LoE:IVb*

OR

- Morphine, IV, to a total maximum dose of 10 mg. (See Appendix II, for individual dosing and monitoring for response and toxicity.)

Currently, there is no convincing evidence to support the use of hyoscine in this setting.

For vomiting:

- Metoclopramide, IM, 10 mg 8 hourly.

LoE:IVb

REFERRAL

» In acute setting for suspected or diagnosed obstruction and/or ongoing pain.
» Complicating urinary tract sepsis.
» Recurrent calculi.

References:

[i] Inker LA, Eneanya ND, Coresh J, et al., for the Chronic Kidney Disease Epidemiology Collaboration. New Creatinine- and Cystatin C-Based Equations to Estimate GFR without Race.N Engl J Med. 2021 November 4, 385 (19):1737-1749.

[ii] Eknoyan G, Lameire N. KDIGO 2012 clinical practice guideline for the evaluation and management of chronic kidney disease. Kidney Int Suppl. 2013;3(1):1-150

[iii] Stevens PE, Ahmed SB, Carrero JJ, Foster B, Francis A, Hall RK, Herrington WG, Hill G, Inker LA, Kazancıoğlu R, Lamb E. KDIGO 2024 clinical practice guideline for the evaluation and management of chronic kidney disease. Kidney international. 2024 Apr 1;105(4):S117-314.

[iv] Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group. KDIGO 2024 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease. Kidney Int. 2024 Apr;105(4S):S117-S314. doi: 10.1016/j.kint.2023.10.018. PMID: 38490803.

5 ways to 5 grams | Heart & Stroke Foundation | South Africa [Internet]. Heart & Stroke Foundation | South Africa. 2018 [cited 2024 Aug 1]. Available from: https://heartfoundation.co.za/topical_articles/5-ways-to-5-grams/

Why should I limit the salt in my food? - MyDynamics [Internet]. MyDynamics. 2021 [cited 2024 Aug 1]. Available from: https://www.mydynamics.co.za/nutrition/why-should-i-limit-the-salt-in-my-food/

[v] Rehabilitation support for severe CKD: de Medeiros AIC, Fuzari HKB, Rattesa C, Brandão DC, de Melo Marinho PÉ. Inspiratory muscle training improves respiratory muscle strength, functional capacity and quality of life in patients with chronic kidney disease: a systematic review. J Physiother. 2017 Apr;63(2):76-83. https://pubmed.ncbi.nlm.nih.gov/28433237/

[vi] Enalapril, oral (maximum daily dose of 40 mg): Joint Formulary Committee. British National Formulary. London: BMJ Group and Pharmaceutical Press; 2020.

[vii] ACE-inhibitor (e.g. enalapril): South African Renal Society Recommendations for the early detection and management of CKD in South Africa. http://www.sa-renalsociety.org/guidelines

ACE-inhibitor (e.g. enalapril): The National Kidney Foundation Kidney Disease Outcomes Quality Initiative (KDOQI) Clinical Practice Guidelines for Chronic Kidney Disease: Evaluation, Classification, and Stratification PART 9. Approach to chronic kidney disease using these guidelines. https://www.kidney.org/professionals/guidelines

ACE-inhibitor (e.g. enalapril): South African Renal Society Guidelines for the Optimal Care of Patients on Chronic Dialysis in South Africa, revised 2011. http://www.sa-renalsociety.org/guidelines

[viii] Angiotensin II receptor blocker (e.g. Losartan): South African Renal Society Recommendations for the Early detection and management of CKDin South Africa. http://www.sa-renalsociety.org/guidelines

Angiotensin II receptor blocker (e.g. Losartan): The National Kidney Foundation Kidney Disease Outcomes Quality Initiative (KDOQI) Clinical Practice Guidelines for Chronic Kidney Disease: Evaluation, Classification, and Stratification PART 9. Approach to chronic kidney disease using these guidelines. https://www.kidney.org/professionals/guidelines

Angiotensin II receptor blocker (e.g. Losartan): South African Renal Society Guidelines for the Optimal Care of Patients on Chronic Dialysis in South Africa, revised 2011. http://www.sa-renalsociety.org/guidelines

[ix] Angiotensin II receptor blocker (angioedema): Caldeira D, David C, Sampaio C. Tolerability of angiotensin-receptor blockers in patients with intolerance to angiotensin-converting enzyme inhibitors: a systematic review and meta-analysis. Am J Cardiovasc Drugs. 2012 Aug1;12(4):263-77. https://www.ncbi.nlm.nih.gov/pubmed/22587776

Angiotensin II receptor blocker (angioedema): Haymore BR, Yoon J, Mikita CP, Klote MM, DeZee KJ. Risk of angioedema with angiotensin receptor blockers in patients with prior angioedema associated with angiotensin-converting enzyme inhibitors: a meta-analysis. Ann Allergy Asthma Immunol. 2008 Nov;101(5):495-9. https://www.ncbi.nlm.nih.gov/pubmed/19055203

Angiotensin II receptor blocker (angioedema): Makani H, Messerli FH, Romero J, Wever-Pinzon O, Korniyenko A, Berrios RS, Bangalore S. Meta-analysis of randomized trials of angioedema as an adverse event of renin-angiotensin system inhibitors. Am J Cardiol. 2012 Aug 1;110(3):383-91. https://www.ncbi.nlm.nih.gov/pubmed/22521308

[x] Metformin: National Department of Health, Essential Drugs Programme: Primary Health Care STGs and EML, draft. https://www.knowledgehub.org.za/content/standard-treatment-guidelines-and-essential-medicines-list

Metformin: The Society for Endocrinology, Metabolism and Diabetes of South Africa Type 2 Diabetes Guidelines Expert Committee. The 2017 SEMDSA Guideline for the Management of Type 2 Diabetes Guideline Committee. JEMDSA 2017; 21(1)(Supplement 1): S1-S196.

Metformin: Canadian Diabetes Association Clinical Practice Guidelines Expert Committee. Canadian Diabetes Association 2013 Clinical Practice Guidelines for the Prevention and Management of Diabetes in Canada. *Can J Diabetes* 2013;37(suppl 1):S1-S212. http://www.ncbi.nlm.nih.gov/pubmed/24070961

Metformin: NICE Clinical Guideline 87: Type 2 diabetes - The management of type 2 diabetes, 2009, 2014. www.nice.org.uk/Guidance/CG87

Metformin: Aronoff, Bennett et al. Drug Prescribing in Renal Failure: Dosing Guidelines for Adults and Children, 5th Edition. American College of Physicians. United States of America, 2007.

Metformin: Lipska KJ, Bailey CJ, Inzucchi SE. Use of metformin in the setting of mild-to-moderate renal insufficiency. Diabetes Care. 2011 Jun;34(6):1431-7. http://www.ncbi.nlm.nih.gov/pubmed/21617112

Orloff et al. Safety and efficacy of metformin in patients with reduced renal function: a systematic review. Diabetes Obes Metab 2021. 23(9): 2035-2047.

Salpeter SR, Greyber E, Pasternak GA, Salpeter EE. Risk of fatal and nonfatal lactic acidosis with metformin use in type 2 diabetes mellitus. Cochrane Database Syst Rev. 2010 Apr 14;2010(4):CD002967. doi: 10.1002/14651858.CD002967.pub4. PMID: 20393934; PMCID: PMC7138050.

[xi] South African Medicines Formulary, 14th Edition. Division of Clinical Pharmacology. University of Cape Town, 2022.

[xii] Mudge DW, Johnson DW, Hawley CM, Campbell SB, Isbel NM, van Eps CL, Petrie JJ. Do aluminium-based phosphate binders continue to have a role in contemporary nephrology practice? BMC Nephrol. 2011 May 13;12:20. doi: 10.1186/1471-2369-12-20. PMID: 21569446; PMCID: PMC3107169.

[xiii] Calciferol, oral: Malabanan et al. Redefining Vit D deficiency. Lancet 1998, 351: 805-806. https://www.ncbi.nlm.nih.gov/pubmed/9519960

[xiv] Erythropoetin, parenteral (simulataneous administration with iron in CKD): Palmer SC, Saglimbene V, Mavridis D, Salanti G, Craig JC, Tonelli M, Wiebe N, Strippoli GF. Erythropoiesis-stimulating agents for anaemia in adults with chronic kidney disease: a network meta-analysis. Cochrane Database Syst Rev. 2014 Dec 8;(12):CD010590. https://www.ncbi.nlm.nih.gov/pubmed/25486075

Erythropoetin, parenteral (simultaneous administration with iron in CKD): Macdougall IC, White C, Anker SD, Bhandari S, Farrington K, Kalra PA, McMurray JJV, Murray H, Tomson CRV, Wheeler DC, Winearls CG, Ford I; PIVOTAL Investigators and Committees. Intravenous Iron in Patients Undergoing Maintenance Hemodialysis. N Engl J Med. 2019 Jan 31;380(5):447-458. https://www.ncbi.nlm.nih.gov/pubmed/30365356

Erythropoetin, parenteral (simultaneous administration with iron in CKD): Kidney disease: improving global outcomes (KDIGO) anemia work group. KDIGO clinical practice guideline for anemia in chronic kidney disease. Kidney Int Suppl. 2012;2:279–335. https://kdigo.org/wp-content/uploads/2016/10/KDIGO-2012-Anemia-Guideline-English.pdf

[xv] Erythropoiesis-Stimulating Agents (ESA), parenteral: Erythropoiesis-Stimulating Agents (Therapeutic review): National Department of Health: Affordable Medicines, EDP-Adult Hospital level. Medicine Review: Thrombolytics, therapeutic class for STEMI, May 2022. https://www.knowledgehub.org.za/e-library

Erythropoiesis-Stimulating Agents (ESA), parenteral: South African Medicines Formulary. 12th Edition. Division of Clinical Pharmacology. University of Cape Town, 2016.

[xvi] KDIGO. Clinical practice guideline for the management of glomerular diseases.2021 Available from: https://www.kidney-international.org/action/showPdf?pii=S0085-2538%2821%2900562-7

[xvii] Gaudry S, Hajage D, Martin-Lefevre L, Louis G, Moschietto S, Titeca-Beauport D, La Combe B, Pons B, de Prost N, Besset S, Combes A, Robine A, Beuzelin M, Badie J, Chevrel G, Reignier J, Bohé J, Coupez E, Chudeau N, Barbar S, Vinsonneau C, Forel JM, Thevenin D, Boulet E, Lakhal K, Aissaoui N, Grange S, Leone M, Lacave G, Nseir S, Poirson F, Mayaux J, Asehnoune K, Geri G, Klouche K, Thiery G, Argaud L, Ricard JD, Quenot JP, Dreyfuss D. The Artificial Kidney Initiation in Kidney Injury 2 (AKIKI2): study protocol for a randomized controlled trial. Trials. 2019 Dec 16;20(1):726. doi: 10.1186/s13063-019-3774-9. PMID: 31843007; PMCID: PMC6915917.

[xviii] Chothia MY, Chikte U, Zemlin A, Moodley D, Fitchat N, Wessels A, van Vuuren E, Davids T, Davids MR. Outcomes of hospitalised patients with hyperkalaemia at a South African tertiary healthcare centre. EClinicalMedicine. 2022 Aug 1;50.

[xix] Batterink J, Cessford TA, Taylor RA. Pharmacological interventions for the acute management of hyperkalaemia in adults. Cochrane Database Syst Rev. 2015 Oct 29;10(10):CD010344. doi: 10.1002/14651858.CD010344.pub2. PMID: 35658162; PMCID: PMC9578550.

[xx] Potassium chloride, oral: South African Medicines Formulary. 14th Edition. Division of Clinical Pharmacology. University of Cape Town, 2022.

[xxi] Potassium chloride, oral: South African Medicines Formulary. 14th Edition. Division of Clinical Pharmacology. University of Cape Town, 2022.

Potassium chloride, oral: Rastegar A, Soleimani M. Hypokalaemia and hyperkalaemia. Postgrad Med J. 2001 Dec;77(914):759-64. Review. Erratum in: Postgrad Med J 2002 Feb;78(916):126. Rastergar A [corrected to Rastegar A]. http://www.ncbi.nlm.nih.gov/pubmed/8250319

Potassium chloride, oral: Wong KC, Schafer PG, Schultz JR. Hypokalemia and anesthetic implications. AnesthAnalg. 1993 Dec;77(6):1238-60. Review. Erratum in: AnesthAnalg 1994 May;78(5):1035. http://www.ncbi.nlm.nih.gov/pubmed/8250319

[xxii] Potassium chloride, IV: South African Medicines Formulary. 14th Edition. Division of Clinical Pharmacology. University of Cape Town, 2022.

Potassium chloride, IV (monitoring): Tsuji H, Venditti FJ Jr, Evans JC, Larson MG, Levy D. The associations of levels of serum potassium and magnesium with ventricular premature complexes (the Framingham Heart Study). Am J Cardiol. 1994 Aug 1;74(3):232-5. https://www.ncbi.nlm.nih.gov/pubmed/7518645

Potassium chloride, IV (monitoring): Hoes AW, Grobbee DE, Peet TM, Lubsen J. Do non-potassium-sparing diuretics increase the risk of sudden cardiac death in hypertensive patients? Recent evidence. Drugs. 1994 May;47(5):711-33. https://www.ncbi.nlm.nih.gov/pubmed/7520854

[xxiii] Dextrose 5%, IV: Adrogué HJ, Madias NE. Hypernatremia. N Engl J Med. 2000 May 18;342(20):1493-9. Review. http://www.ncbi.nlm.nih.gov/pubmed/10816188

Dextrose 5%, IV: Lindner G, Funk GC. Hypernatremia in critically ill patients. J Crit Care. 2013 Apr;28(2):216.e11-20. http://www.ncbi.nlm.nih.gov/pubmed/22762930

[xxiv] Verbalis JG, Goldsmith SR, Greenberg A, Korzelius C, Schrier RW, Sterns RH, Thompson CJ. Diagnosis, evaluation, and treatment of hyponatremia: expert panel recommendations. Am J Med. 2013 Oct;126(10 Suppl 1):S1-42. doi: 10.1016/j.amjmed.2013.07.006. PMID: 24074529.

Spasovski G, Vanholder R, Allolio B, Annane D, Ball S, Bichet D, Decaux G, Fenske W, Hoorn EJ, Ichai C, Joannidis

M, Soupart A, Zietse R, Haller M, van der Veer S, Van Biesen W, Nagler E. Clinical practice guideline on diagnosis and treatment of hyponatraemia. Intensive Care Med. 2014 Mar;40(3):320-31. doi: 10.1007/s00134-014-3210-2. Epub 2014 Feb 22. Erratum in: Intensive Care Med. 2014 Jun;40(6):924. Hoorn, Ewout [corrected to Hoorn, Ewout J]. PMID: 24562549.

[xxv] Hyponatraemia algorithm: Adrogué HJ, Madias NE. Hyponatremia. N Engl J Med. 2000 May 25;342(21):1581-9. http://www.ncbi.nlm.nih.gov/pubmed/10816188

[xxvi] Furosemide, oral: Adrogué HJ, Madias NE. Hyponatremia. N Engl J Med. 2000 May 25;342(21):1581-9. Review. http://www.ncbi.nlm.nih.gov/pubmed/10824078

[xxvii] Sodium chloride, 0.9%, IV: Adrogué HJ, Madias NE. Hyponatremia. N Engl J Med. 2000 May 25;342(21):1581-9. Review. http://www.ncbi.nlm.nih.gov/pubmed/10824078

[xxviii] Praziquantel: National Department of Health, Essential Drugs Programme: Primary Health Care STGs and EML, draft. http://www.health.gov.za/

[xxix] Fosfomycin, oral: Falagas ME, Vouloumanou EK, Togias AG, Karadima M, Kapaskelis AM, Rafailidis PI, Athanasiou S. Fosfomycin versus other antibiotics for the treatment of cystitis: a meta-analysis of randomized controlled trials. J Antimicrob Chemother. 2010 Sep;65(9):1862-77. http://www.ncbi.nlm.nih.gov/pubmed/20587612

Fosfomycin, oral: Lewis DA, Gumede LY, van der Hoven LA, de Gita GN, de Kock EJ, de Lange T, Maseko V, Kekana V, Smuts FP, Perovic O. Antimicrobial susceptibility of organisms causing community-acquired urinary tract infections in Gauteng Province, South Africa. S Afr Med J. 2013 Mar 15;103(6):377-81. http://www.ncbi.nlm.nih.gov/pubmed/23725955

[xxx] Gentamicin, parenteral: National Department of Health: Affordable Medicines, EDP-Adult Hospital level. Medicine Review: Gentamicin for uncomplicated UTI, November 2019. https://www.knowledgehub.org.za/content/standard-treatment-guidelines-and-essential-medicines-list

Gentamicin, parenteral:Goodlet KJ, Benhalima FZ, Nailor MD. A Systematic Review of Single-Dose Aminoglycoside Therapy for Urinary Tract Infection: Is It Time To Resurrect an Old Strategy? Antimicrob Agents Chemother. 2018 Dec 21;63(1). pii: e02165-18. https://www.ncbi.nlm.nih.gov/pubmed/30397061

[xxxi] Huttner A, Verhaegh EM, Harbarth S, Muller AE, Theuretzbacher U, Mouton JW. Nitrofurantoin revisited: a systematic review and meta-analysis of controlled trials. J Antimicrob Chemother. 2015 Sep;70(9):2456-64. https://www.ncbi.nlm.nih.gov/pubmed/26066581

Nitrofurantoin, oral: Zalmanovici Trestioreanu A, Green H, Paul M, Yaphe J, Leibovici L. Antimicrobial agents for treating uncomplicated urinary tract infection in women. Cochrane Database Syst Rev. 2010 Oct 6;(10):CD007182. https://www.ncbi.nlm.nih.gov/pubmed/20927755

Nitrofurantoin, oral: Lewis DA, Gumede LY, van der Hoven LA, de Gita GN, de Kock EJ, de Lange T, Maseko V, Kekana V, Smuts FP, Perovic O. Antimicrobial susceptibility of organisms causing community-acquired urinary tract infections in Gauteng Province, South Africa. S Afr Med J. 2013 Mar 15;103(6):377-81. http://www.ncbi.nlm.nih.gov/pubmed/23725955

Nitrofurantoin, oral: Nordeng H, Lupattelli A, Romøren M, Koren G. Neonatal outcomes after gestational exposure to nitrofurantoin. Obstet Gynecol. 2013 Feb;121(2 Pt 1):306-13. http://www.ncbi.nlm.nih.gov/pubmed/23344280

[xxxii] Ciprofloxacin, oral: Lewis DA, Gumede LY, van der Hoven LA, de Gita GN, de Kock EJ, de Lange T, Maseko V, Kekana V, Smuts FP, Perovic O. Antimicrobial susceptibility of organisms causing community-acquired urinary tract infections in Gauteng Province, South Africa. S Afr Med J. 2013 Mar 15;103(6):377-81.http://www.ncbi.nlm.nih.gov/pubmed/23725955

[xxxiii] Ciprofloxacin, oral (caution - concomitant use with ACE-inhibitor/ARB): Savage R. Ciprofloxacin, enalapril and acute kidney injury: Strengthening of a drug Interaction signal. WHO Pharmaceuticals Newsletter : 16-21, No. 1, 201. http://www.who.int/medicines/publications/WHO-Pharmaceuticals_Newsletter_No1-2018.pdf?ua=1

Ciprofloxacin, oral (caution - concomitant use with ACE-inhibitor/ARB): Bird ST, Etminan M, Brophy JM, Hartzema AG, Delaney JA. Risk of acute kidney injury associated with the use of fluoroquinolones. CMAJ. 2013 Jul 9;185(10):E475-82. https://www.ncbi.nlm.nih.gov/pubmed/23734036

[xxxiv] Fosfomycin, oral: Falagas ME, Vouloumanou EK, Togias AG, Karadima M, Kapaskelis AM, Rafailidis PI, Athanasiou S. Fosfomycin versus other antibiotics for the treatment of cystitis: a meta-analysis of randomized controlled trials. J Antimicrob Chemother. 2010 Sep;65(9):1862-77. http://www.ncbi.nlm.nih.gov/pubmed/20587612

Fosfomycin, oral: Lewis DA, Gumede LY, van der Hoven LA, de Gita GN, de Kock EJ, de Lange T, Maseko V, Kekana V, Smuts FP, Perovic O. Antimicrobial susceptibility of organisms causing community-acquired urinary tract infections in Gauteng Province, South Africa. S Afr Med J. 2013 Mar 15;103(6):377-81. http://www.ncbi.nlm.nih.gov/pubmed/23725955

[xxxv] Huttner A, Verhaegh EM, Harbarth S, Muller AE, Theuretzbacher U, Mouton JW. Nitrofurantoin revisited: a systematic review and meta-analysis of controlled trials. J Antimicrob Chemother. 2015 Sep;70(9):2456-64. https://www.ncbi.nlm.nih.gov/pubmed/26066581

Nitrofurantoin, oral: Zalmanovici Trestioreanu A, Green H, Paul M, Yaphe J, Leibovici L. Antimicrobial agents for treating uncomplicated urinary tract infection in women. Cochrane Database Syst Rev. 2010 Oct 6;(10):CD007182. https://www.ncbi.nlm.nih.gov/pubmed/20927755

Nitrofurantoin, oral: Lewis DA, Gumede LY, van der Hoven LA, de Gita GN, de Kock EJ, de Lange T, Maseko V, Kekana V, Smuts FP, Perovic O. Antimicrobial susceptibility of organisms causing community-acquired urinary tract infections in Gauteng Province, South Africa. S Afr Med J. 2013 Mar 15;103(6):377-81. http://www.ncbi.nlm.nih.gov/pubmed/23725955

Nitrofurantoin, oral: Nordeng H, Lupattelli A, Romøren M, Koren G. Neonatal outcomes after gestational exposure to nitrofurantoin. Obstet Gynecol. 2013 Feb;121(2 Pt 1):306-13. http://www.ncbi.nlm.nih.gov/pubmed/23344280

[xxxvi] Urinary tract infection definitions: Johansen TE, Botto H, Cek M, Grabe M, Tenke P, Wagenlehner FM, Naber KG. Critical review of current definitions of urinary tract infections and proposal of an EAU/ESIU classification

system. Int J Antimicrob Agents. 2011 Dec;38 Suppl:64-70. https://pubmed.ncbi.nlm.nih.gov/22018988/

[xxxvii] Ceftriaxone, IM: National Department of Health, Essential Drugs Programme: Primary Health Care STGs and EML, 2018. http://www.health.gov.za/

Ceftriaxone, IM: Newman LM, Moran JS, Workowski KA. Update on the management of gonorrhea in adults in the United States. Clin Infect Dis. 2007 Apr 1;44Suppl 3:S84-101.Review. http://www.ncbi.nlm.nih.gov/pubmed/17342672

Ceftriaxone, IM: Workowski KA, Berman S; Centers for Disease Control and Prevention (CDC). Sexually transmitted diseasestreatment guidelines, 2010.MMWR Recomm Rep. 2010 Dec 17;59(RR-12):1-110. Erratum in: MMWR Recomm Rep. 2011 Jan14;60(1):18. Dosage error in article text. http://www.cdc.gov/std/treatment/2010/

[xxxviii] Azithromycin, oral: National Department of Health, Essential Drugs Programme: Primary Health Care STGs and EML, 2018. http://www.health.gov.za/

Azithromycin, oral: Azithromycin: Lau CY, Qureshi AK. Azithromycin versus doxycycline for genital chlamydial infections: a meta-analysis of randomized clinical trials. Sex Transm Dis. 2002 Sep;29(9):497-502. http://www.ncbi.nlm.nih.gov/pubmed/12218839

[xxxix] Alpha-blocker: Djavan B, Marberger M. A meta-analysis on the efficacy and tolerability of alpha1-adrenoceptor antagonists in patients with lower urinary tract symptoms suggestive of benign prostatic obstruction. Eur Urol. 1999;36(1):1-13.http://www.ncbi.nlm.nih.gov/pubmed/10364649

Alpha-blocker: South African Medicines Formulary. 14th Edition. Division of Clinical Pharmacology. University of Cape Town, 2022.

Fawzy A, Vashi V, Chung M, Dias N, Gaffney M. Clinical correlation of maximal urinary flow rate and plasma doxazosin concentrations in the treatment of benign prostatic hyperplasia. Multicenter Study Group. Urology. 1999 Feb;53(2):329-35.https://pubmed.ncbi.nlm.nih.gov/9933049/

[xl] Oxybutynin, oral: South African Medicines Formulary. 14th Edition. Division of Clinical Pharmacology. University of Cape Town, 2022.

[xli] NSAID, oral: Afshar K, Jafari S, Marks AJ, Eftekhari A, MacNeily AE. Nonsteroidal anti-inflammatory drugs (NSAIDs) and non-opioids for acute renal colic. Cochrane Database Syst Rev. 2015 Jun 29;6:CD006027. http://www.ncbi.nlm.nih.gov/pubmed/26120804

CHAPTER 8

ENDOCRINE DISORDERS

8.1 ACROMEGALY

E22.0

DESCRIPTION

Acromegaly is a disorder caused by growth hormone (GH) hypersecretion usually due to a pituitary adenoma, with associated morbidities, and increased mortality.
This condition should be managed at a tertiary centre.
Transsphenoidal adenomectomy is the accepted form of primary therapy.
Radiotherapy post operatively may be required. In addition, adjunctive medical therapy may be required in specific circumstances.

Investigations

If the diagnosis is suspected, screening should be done in consultation with a specialist.

REFERRAL

All patients with suspected acromegaly to a hospital with endocrine and neurosurgery facilities.

8.2 ADRENAL INSUFFICIENCY (ADDISON DISEASE)

E27.1/E27.2

DESCRIPTION

Primary adrenocortical insufficiency.

Clinical presentation

Acute crisis: (not all symptoms and signs may occur in a particular patient, so a high index of suspicion is needed).

- » hypotension
- » fever
- » GIT disturbances
- » dehydration
- » weakness
- » depressed mentation
- » hypoglycaemia
- » hyponatraemia
- » hyperkalaemia
- » acidosis

Chronic:

- » hyperpigmentation
- » weakness and fatigue
- » loss of weight
- » postural dizziness
- » arthralgia
- » GIT disturbances
- » hypotension
- » hypoglycaemia
- » hyponatraemia
- » hyperkalaemia

Always consider this diagnosis in a thin, hypotensive, hypoglycaemic patient, or during stress e.g. sepsis. **The combination of hyponatraemia and hyperkalaemia should suggest possible primary adrenal insufficiency.**
Note: Treatment of suspected acute adrenal failure should never be delayed to obtain results of diagnostic procedures.

Investigations

08h00 serum cortisol level (or at time of presentation in acute crisis):

- >500 nmol/L: virtually excludes the diagnosis
- with newer assays cortisol concentrations >450 nmol/L are acceptable to exclude hypoadrenalism
- 100–450 nmol/L is indeterminate and may require an adrenocorticotropic hormone (ACTH) stimulation test:

- ACTH depot, IM, 1 mg with blood sampling at 60 minutes.
  - Post ACTH, serum cortisol level normal value: >550 nmol/L or double the pre-test level.

LoE:III[i]

GENERAL MEASURES

All patients with confirmed hypoadrenalism.
Investigate for other causes such as sepsis and treat accordingly.

MEDICINE TREATMENT

Acute crisis

E27.2

Before administering hydrocortisone, ensure blood samples are taken for serum cortisol and plasma ACTH, if feasible.

- Hydrocortisone, IV, 100 mg 6 hourly.
  - Change to oral maintenance therapy once stable. *LoE:III[ii]*

To maintain adequate intravascular volume guided by blood pressure:

- Sodium chloride 0.9%, IV with regular glucose monitoring, and 50% dextrose boluses if required.
  - Beware of fluid overload if the combination of sodium chloride 0.9%/dextrose 5% is utilised.
  - The fluid deficit is often several litres. *LoE:III[iii]*

Monitor glucose levels closely and treat hypoglycaemia if present.
Note: All suspected cases should be referred for full evaluation, prior to chronic maintenance therapy.

Chronic

As maintenance therapy:

- Hydrocortisone, oral.
  - Start with 10 mg in the morning and 5 mg at night.

- Increase the dose according to clinical response up to 20 mg in the morning and 10 mg at night.
- In patients requiring a midday dose, a suggested regimen is 10 mg in the morning, 5 mg at midday and 5 mg in the early evening.

OR *LoE:III*

- Corticosteroids (intermediate-acting) e.g.:
- Prednisone, oral.
  - Start with 5 mg daily.
  - Increase to maximum of 7.5 mg daily, if necessary. *LoE:III[iv]*

For patients who have symptoms of mineralocorticoid deficiency:

- Fludrocortisone, oral, 50–100 mcg daily may be required to normalise the potassium and to reduce postural hypotension in primary hypoadrenalism.
  - Titrate dose of fludrocortisone in consultation with a specialist.

LoE:III[v]

Monitor response to therapy with:
» Symptoms: improvement in fatigue and GIT disturbances.
» Blood pressure: normotensive and no postural drop.
» Electrolytes: normal Na+ and K+.

During times of severe "stress" i.e. acute illness, surgery, trauma, etc.:

- Hydrocortisone, IV, 100 mg 6 hourly. *LoE:III[vi]*

Minor stressors e.g.: Influenza, diarrhoeal illness, chest infections and dental procedures warrant doubling of the doses of hydrocortisone for the duration of illness and gradual tapering back to usual dose.

REFERRAL
All suspected cases, for full evaluation.

8.3 ANDROGEN DEFICIENCY
E29.1

DESCRIPTION
Reduced testosterone due to hypothalamic/pituitary hypofunction or primary testicular failure.

Investigations
» Morning (08h00–09h00) serum total testosterone.
» LH and FSH

	Serum testosterone	LH and FSH
Primary testicular failure	Below normal	Above normal
Secondary (hypothalamic/pituitary) hypogonadism	Below normal	Normal or below normal

Note: If the serum total testosterone concentration is borderline low repeat the test before replacement therapy is initiated. Don't test during serious illness.

» Measure serum prolactin
» Sperm count, if infertility is a consideration.
» Further investigations to determine cause to be undertaken after referral; consult a specialist.

MEDICINE TREATMENT

Screen hypogonadal men for prostate cancer before beginning testosterone replacement. Testosterone therapy can induce prostatic hypertrophy, polycythaemia, liver dysfunction, sleep apnoea and hyperlipidaemia. Baseline investigations for these are required prior to initiation of therapy and long-term surveillance is required.
Individualise dosage and review doses based on clinical response.

- Testosterone cypionate, deep IM, 200–300 mg every 2–4 weeks.
  - Monitor patients for prostate cancer during treatment.
  - Monitor haematocrit. If haematocrit ≥ 54%, stop testosterone therapy.

LoE:I[vii]

8.4 CUSHING SYNDROME

E24.0-4/E24.8-9

DESCRIPTION

Cushing syndrome is an illness resulting from excess cortisol secretion or exogenous glucocorticoid administration. Cushing disease is hypercortisolism secondary to an ACTH-secreting pituitary tumour.

Investigations

Low dose overnight dexamethasone suppression test (or when unavailable, betamethasone 1 mg equivalent to dexamethasone 1 mg).

- Dexamethasone, oral, 1 mg.
  - Administer at 23:00.
  - Measure plasma cortisol at 8:00, the next morning after breakfast.
  - In people with normal pituitary and adrenal function morning cortisol will be suppressed to <50 nmol/L.
  - Refer if cortisol levels >50 nmol/L.

LoE:III[viii]

GENERAL MEASURES

Check for hypertension and diabetes and treat accordingly.
Check potassium.

REFERRAL
All cases for investigation of aetiology and appropriate management.

8.5 DIABETES MELLITUS

DESCRIPTION
Types of diabetes:
» Type 1.
» Type 2.
» Other specific types, including pancreatic diabetes mellitus.
» Gestational diabetes mellitus: See Section 6.2: Diabetes mellitus in pregnancy.

GENERAL MEASURES
All patients require lifestyle modification.
Type 2 diabetes mellitus patients: weight loss if weight exceeds ideal weight.
Correct meal/energy distribution.
Moderate or no alcohol intake.
Encourage smoking cessation.
Increase physical activity, aim for 30 minutes per day 5 times a week.
Education about foot care is essential.
Manage comorbid depression. See Section 15.3.1: Depressive disorders.

Diagnosis
» In patients with symptoms of hyperglycaemia and any one of the following criteria:
  - Random plasma glucose ≥11.1 mmol/l; or
  - Fasting plasma glucose ≥7.0 mmol/l; or
  - 2-hour plasma glucose in a 75 g oral glucose tolerance test ≥11.1 mmol/l.

» In asymptomatic patients any one of the following criteria, confirmed by a repeat test on a separate day within 2 weeks:
  - Fasting plasma glucose ≥7.0 mmol/l; or
  - 2-hour plasma glucose in a 75 g oral glucose tolerance test ≥11.1 mmol/l.

LoE:III[ix]

Classification:
After diabetes mellitus has been diagnosed, attempts must be made to classify the patient as type 1, type 2 or one of the other specific types (including pancreatic diabetes, genetic syndromes, infection and other causes). For management of gestational diabetes, see Section 6.2: Diabetes mellitus in pregnancy.

Monitoring

At every visit: *LoE:III[x]*

» Finger-prick blood glucose.
» Weight and calculation of body mass index.
» Waist circumference.
» Blood pressure.

Baseline:

» Serum creatinine concentration (and calculate estimated glomerular filtration rate (eGFR)).
» Serum potassium concentration, if on ACE-inhibitor or eGFR <30 mL/minute.
» Urine protein by dipstick.
  – If dipstick negative, request ACR, unless already on an ACE-inhibitor - microalbuminuria is defined as 2.5 to 25 mg/mmol in men, and 3.5 to 35 mg/mmol in women (see Section 8.7.2: Diabetic kidney disease).
  – If dipstick positive, see Section 8.7.2: Diabetic kidney disease.
» Blood lipids (fasting total cholesterol, triglycerides, HDL and LDL cholesterol).
» Foot examination.
» Eye examination to look for retinopathy.
» Waist circumference.

Measure HbA1c:

» 6-monthly in patients who meet treatment goals, and
» 3-monthly in patients whose control is sub-optimal or if therapy has changed, until stable.

Note: Monitoring of HbA1c implies that active clinical management will be implemented if the level is sub-optimal.

Annually:

» Serum creatinine concentration (and calculate eGFR).
» Serum potassium concentration (if on ACE-inhibitor/ eGFR <30 mL/minute).
» Urine protein by dipstick. *LoE:III[xi]*
  – If dipstick negative, request ACR, unless already on an ACE-inhibitor - microalbuminuria is defined as 2.5 to 25 mg/mmol in men, and 3.5 to 35 mg/mmol in women (see Section 8.7.2: Diabetic kidney disease).
  – If dipstick positive, see Section 8.7.2: Diabetic kidney disease.
» Eye examination to look for retinopathy.
» Foot examination.
» Assessment for peripheral neuropathy.
» Oral and dental examination.
» Assessment for macrovascular disease.
» Resting ECG.

TARGETS FOR CONTROL

Glycaemic targets for control:

Patient type	Target HbA1c	Target FPG*	Target PPG*
• Young, low risk • Newly diagnosed • No CVS disease	<6.5%	4.0–7.0 mmol/L	4.4–7.8 mmol/L
• Majority of patients	<7.0%	4.0–7.0 mmol/L	5.0–10.0 mmol/L
• Elderly • High risk • Hypoglycaemic unawareness • Poor short-term prognosis	<7.5%	4.0–7.0 mmol/L	<12.0 mmol/L

*FPG: fasting plasma glucose; PPG: post prandial plasma glucose.

Non-glycaemic targets:

» BMI ≤25 kg/m^2.
» BP ≤140/90 mmHg and ≥120/70 mmHg.

In the elderly, the increased risk of hypoglycaemia must be weighed against the potential benefit of reducing microvascular and macrovascular complications.

In patients with severe target organ damage, therapy should be tailored on an individual patient basis and should focus on avoiding hypoglycaemia.

REFERRAL

» Inability to achieve optimal metabolic control.
» Complications that cannot be managed on site, especially ophthalmic, e.g. cataracts and proliferative retinopathy.
» Recurrent severe hypoglycaemia.

8.5.1 TYPE 2 DIABETES MELLITUS

E11.0-9/E12.0-9/E13.0-9/E14.0-9

Management includes:

» Treatment of hyperglycaemia.
» Treatment of hypertension and dyslipidaemia after risk-assessment. See Section 3.6: Hypertension.
» Prevention and treatment of microvascular complications.
» Prevention and treatment of macrovascular complications.

MEDICINE TREATMENT

Oral blood glucose lowering drugs

Metformin is the preferred initial medicine and is added to the combination of dietary modifications and physical activity/exercise. If metformin, in maximal dose, with diet and exercise fails to lower HbA1c to target, a second agent should be added. This second agent may be either a sulphonylurea, or basal insulin. The specific indication is dependent on individual circumstances.

If a combination of two agents fails to lower HbA1c to target, a third agent is added. The preferential sequence of agents to use is metformin, followed by the addition of sulphonylurea, followed by the addition of basal insulin.

If the combination of two oral agents and basal insulin fails to lower HbA1c to target, or if other reasons to adjust therapy exist (such as nocturnal hypoglycaemia), then intensified insulin therapy in consultation with a specialist is required (either twice daily pre-mix, or basal-bolus therapy) and sulphonylureas are discontinued.

Note: Secondary failure of oral agents occurs in about 5–10% of patients annually.

Metformin

- Metformin, oral, 500 mg twice daily with meals.
  - Adjust dose based on fasting blood glucose levels and/or HbA1c to a maximum dose of 850 mg 8 hourly.
  - Monitor renal function. *LoE:I*[xii]
  - Dose-adjust in renal impairment as follows:

eGFR	Metformin dose
» eGFR >60 mL/min:	Normal daily dose (see above).
» eGFR 45–60 mL/min:	Standard dose, measure eGFR 3–6 monthly.
» eGFR 30–45 mL/min:	Maximum dose 1 g per day; measure eGFR 3–6 monthly.
» eGFR <30 mL/min:	Stop metformin.

  - Contra-indicated in:
    - renal impairment i.e. eGFR <30 mL/minute, *LoE:III*[xiii]
    - uncontrolled congestive cardiac failure,
    - severe liver disease,
    - patients with significant respiratory compromise, or
    - peri-operative cases.

Sulphonylurea derivatives: glimepiride or glibenclamide.

- Glimepiride, oral, 1 mg daily.
  - Titrate the dose by 1 mg at weekly intervals up to 6 mg daily (according to blood glucose levels). *LoE:III*[xiv]
  - Usual dose: 4 mg daily.
  - Maximum dose: 8 mg daily.

OR

- Glibenclamide, oral, 2.5 mg daily 30 minutes before breakfast.

- Titrate dose slowly depending on HbA1c and/or fasting blood glucose levels to 15 mg daily.
- When ≥7.5 mg per day is needed, divide the total daily dose into 2, with the larger dose in the morning.
- Avoid in the elderly and patients with renal impairment (i.e. eGFR <60 mL/minute).

LoE:III[xv]

Oral agents should not be used in type 1 diabetes and should be used with caution in liver and renal impairment.
Metformin should be dose adjusted in renal impairment.
Monitor patients on sulphonylurea derivatives and concomitant rifampicin and dose-adjust sulphonylurea as required. When rifampicin is discontinued, monitor for risk of hypoglycaemia and dose adjustment is required, particularly in the elderly.

Monitor serum creatinine and estimated eGFR three monthly in patients with kidney disease.

Insulin therapy in type 2 diabetes

Indications for insulin therapy:

» Inability to control blood glucose pharmacologically, i.e. combination/substitution insulin therapy.
» Temporary use for major stress, e.g. surgery, medical illness.
» Severe kidney or liver disease.
» Pregnancy.

Note:

» At initiation of insulin therapy, give appropriate advice on self-blood glucose monitoring (SBGM) and diet.
» It is advisable to maintain all patients on metformin once therapy with insulin has been initiated.

Insulin type	Starting dose	Increment	Max. daily dose
Add on therapy: • Intermediate to long-acting insulin	10 units, (or 0.3 units/kg/day), in the evening before bedtime, but not after 22h00.	If the starting dose is not effective increase by 2-4 units per dose every 3 to 7 days until fasting glucose is in the target range.	Refer if recurrent hypoglycaemia occurs and targets for control are not met.
Substitution therapy: • Biphasic insulin (30/70 mix)	Total daily dose: 0.3 units/kg/day divided as follows: • 2/3 of total daily dose 30 minutes before breakfast. • 1/3 of total daily dose 30 minutes	4 units weekly. First increment is added to dose before breakfast.	Refer if recurrent hypoglycaemia occurs and targets for control are not met.

Insulin type	Starting dose	Increment	Max. daily dose
	before supper. *LoE:III*[xvi]	Second increment is added to dose before supper.	
Basal bolus insulin therapy	Start with 0.4 to 0.6 units/kg and divide this total daily dose into 50% basal and 50% bolus, using equal pre-meal doses	Basal insulin is adjusted according to fasting glucose levels and bolus insulin is adjusted according to pre- and post-meal glucose, using the patient's home glucose record as a guide.	Refer if recurrent hypoglycaemia occurs and targets for control are not met.

Also see insulin protocols as in Section 8.5.2: Type 1 diabetes mellitus.

LoE:III[xvii]

Note: Insulin requirements decrease in patients with chronic renal impairment. In these situations, blood glucose monitoring must be done regularly (at least daily) in order to reduce the dose appropriately, reducing the risk of hypoglycaemia.

To reduce cardiovascular risk
See Section 8.8: Dyslipidaemia.

Renal impairment
If urine ACR >2.5 mg/mmoL (men) or >3.5 mg/mmoL (women):
Start treatment with a low dose of ACE-inhibitor and titrate up to the maximum tolerated dose.

ADD *LoE:I*[xviii]

- ACE-inhibitor, e.g.:
- Enalapril, oral.
  - Start with 5 mg 12 hourly and titrate to 20 mg 12 hourly, if tolerated (depending on BP and ACR). *LoE:III*[xix]

See Section 7.1.1: Chronic Kidney Disease.

If an ACE-inhibitor is not tolerated due to intractable cough, consider an angiotensin II receptor blocker. See Section 7.1.1: Chronic Kidney Disease.

8.5.2 TYPE 1 DIABETES MELLITUS

E10.0-9/ E12.0-9/E13.0-9/E14.0-9

Management includes:
» Maintenance of glycaemic control within acceptable limits.
» Prevention of chronic complications.
» Prevention of acute complications, e.g. hyperglycaemic and hypoglycaemic coma.

Insulin preparations

- Insulin, short acting SC, three times daily, 30 minutes before meals:
  Regular human insulin.
  Onset of action: 30 minutes.
  Peak action: 2–5 hours.
  Duration of action: 5–8 hours.
- Insulin, intermediate acting, SC, once or twice daily, usually at night, not later than 22h00.
  Onset of action: 1–3 hours.
  Peak action: 6–12 hours.
  Duration of action: 16–24 hours.
- Insulin, biphasic, SC, once or twice daily.
  Mixtures of regular human insulin and NPH insulin in different proportions, e.g. $^{30}/_{70}$.
  Onset of action: 30 minutes.
  Peak action: 2–12 hours.
  Duration of action: 16–24 hours.

Selection of insulin regimen

Basal bolus regimen

All type 1 diabetics should preferentially be managed with combined intermediate-acting (basal) and short-acting insulin (bolus), the so-called basal bolus regimen. This consists of pre-meal short-acting insulin and bedtime intermediate-acting insulin not later than 22h00.

Insulin doses

The initial total daily insulin dose:

- 0.6 units/kg body weight.

The total dose is divided into:

- 40–50% basal insulin
- The rest of the total daily dose (TDD) is given as bolus insulin split equally before each meal.

Adjust dose on an individual basis.

Alternative regimen where blood glucose cannot be measured frequently by the patient or caregiver: Twice daily insulin

Twice daily pre-mixed insulin, i.e. a mixture of intermediate- or short- acting insulin provides adequate control, when used with at least daily blood glucose monitoring.

Note: Optimal glycaemic control is seldom achieved with this regimen.

LoE:III

Insulin delivery devices

In visually impaired patients prefilled syringes should be used.

Home glucose monitoring

Patients on basal/bolus insulin should measure glucose 3-4 times daily. This may be individualised depending on the clinical need of the patient. *LoE:III*

All patients with type 2 diabetes, on insulin, should be given test strips for home glucose monitoring appropriate for their care plan.
It is important to maximise the value of home glucose monitoring by careful review of home glucose records at each visit and appropriate patient education in terms of self-dose adjustment.

LoE:I[xx]

Glucagon

Type 1 diabetics, who are found to be at high risk of hypoglycaemia because of recurrent episodes, should have a glucagon hypoglycaemia kit and both the patient and their family should be trained to use this emergency therapy.

Repeat prescriptions of glucagon hypoglycaemia kit should only be given if the kit has expired or been utilised.

LoE:III

8.6 DIABETIC EMERGENCIES

Diabetic emergencies includes hypyoglycaemia, diabetic ketoacidosis (DKA) and hyperglycaemic hyperosmolar syndrome (HHS).

8.6.1 HYPOGLYCAEMIA

E10.0-1/E10.6/E11.0-1/E11.6/E12.0-1/E12.0-1/E12.6/E13.0-1/E13.6/E14.0-1/E14.6

Diagnosis: Clinical

Symptoms:

- » Anxiety
- » Palpitations
- » Headaches
- » Sweating
- » Hunger
- » Behavioural changes

Signs:

- » Sweating
- » Tachycardia
- » Bizarre neurological signs
- » Coma
- » Tremor
- » Confusion
- » Seizures

Biochemical

Act on finger prick blood glucose. Confirm with laboratory measurements if uncertain.

TREATMENT

Start immediately.

- Dextrose 50%, rapid IV injection, 50 mL.

Assess clinical status and finger prick glucose level over the next 5–10 minutes.

LoE:III[xxi]

Establish a large bore intravenous line and keep open with:

- Dextrose 10%, IV.

If no clinical response, give a second injection of:

- Dextrose 50%, IV, 50 mL.

To prevent recurrent hypoglycaemia, continue infusion with:

- Dextrose 10%, IV infusion, at a rate of ± 1 L 6 hourly.

Once blood glucose is normal or elevated, and the patient is awake, check blood glucose hourly for several hours, and check serum potassium for hypokalaemia.

If the patient has not regained consciousness after 30 minutes with normal or elevated blood glucose, look for other causes of coma.

Once the patient is awake, give a snack if possible, and **admit** for observation and education etc., to prevent further hypoglycaemic episodes.

> If hypoglycaemia was caused by a sulphonylurea, the patient will require hospitalisation and a prolonged intravenous glucose infusion.
>
> Observe patient for at least 12 hours after glucose infusion has stopped.

Recurrent hypoglycaemia

In cases of recurrent hypoglycaemia consider:

» inappropriate management, e.g. too much insulin or too high dose of sulphonylurea,
» poor meal adherence,
» poor adherence,
» alcohol abuse,
» physical exercise,
» factitious administration of insulin,
» the “honeymoon” period of type 1 diabetes,
» the advent of renal failure,
» hypoglycaemic unawareness, or
» pancreatic diabetes/malabsorption.

Other causes of hypoglycaemia should also be considered e.g. associated Addison’s disease or hypopituitarism.

Recurrent hypoglycaemia may be the cause of hypoglycaemic unawareness, which may occur in patients with type 1 diabetes. The loss of warning symptoms can lead to severe hypoglycaemia. In some cases, this situation can be restored to normal with avoidance of any hypoglycaemia for at least 2–4 weeks.

8.6.2 DIABETIC KETOACIDOSIS (DKA) AND HYPEROSMOLAR HYPERGLYCAEMIC STATE (HHS)

E10.0-1/E11.0-1/E12.0-1/E13.0-1/E14.0-1

Diabetic comas – recognition and clinical profiles

DKA often occurs in younger patients and develops over hours to days. There may be vomiting, abdominal pain and acidotic breathing.

» blood glucose usually <40 mmol/L
» blood ketones are positive
» serum osmolality <350 mOsm/L

Hyperosmolar hyperglycaemic state (HHS) is a syndrome characterised by impaired consciousness, sometimes accompanied by seizures, extreme dehydration and severe hyperglycaemia, that is not accompanied by severe ketoacidosis (pH usually >7.2). It usually occurs in elderly type 2 diabetic patients and develops over days to weeks.

» Blood glucose usually >40 mmol/L.
» Blood ketones usually negative to moderately elevated.
» Urine ketones may be positive.
» Serum osmolality is >320 mOsm/L.

Anion gap = Na – (Cl + HCO_3) (Normal = ± 12: DKA >20).
Calculated serum osmolarity = 2 (Na + K) + glucose + urea.

GENERAL MEASURES

All patients:

» Set up an intravenous line.
» Protect airway and insert a nasogastric tube, if unconscious.
» Monitor urine output.
» Monitor plasma glucose, ketones, urine, electrolytes and venous blood gas.
» Look for precipitating causes, e.g. infection or MI.

MEDICINE TREATMENT

Fluids

Average deficit 6 L, may be as much as 12 L.
If renal or cardiac disease is present, monitor with central venous pressure.
In the absence of renal or cardiac compromise:

- Sodium chloride 0.9%, IV, 15–20 mL/kg in the first hour.
  - Patients <20 years of age: initial volume of 10–20 mL/kg in the 1st hour.
  - Subsequent infusion rate varies from 5–15 mL/kg/hour depending on the clinical condition.
  - Correction of estimated deficits should take place over 24 hours.
  - The volume infused in the first 4 hours should not exceed 50 mL/kg.
  - Fluid therapy thereafter is calculated to replace the estimated deficit in 48 hours, ± 5 mL/kg/hour.
  - Reduction in serum osmolality should not exceed 3 mOsm/kg/hour.

Correct plasma sodium value for blood glucose.
[Rough guide: divide glucose by 3 and add to sodium value.]

If plasma Na^+ >140 mmol/L:
- Sodium chloride 0.45%, IV.

If plasma Na^+ ≤140 mmol/L:
- Sodium chloride 0.9%, IV.

If plasma glucose <15 mmol/L, but ketones still present:
- Dextrose 5% **or** dextrose 10% in sodium chloride 0.9%, IV.

LoE:III[xxii]

Note:
» Adjust fluid volumes according to clinical criteria.
» Cerebral oedema may occur with over-aggressive fluid replacement or rapid sodium change.

Potassium

Potassium will fall on insulin treatment and patients with DKA have potassium depletion even if initial potassium is normal or high.
It is therefore essential to monitor and replace potassium.

Total body deficit 300–1 000 mmol.
(1 ampoule = 20 mmol = 10 mL)

- Potassium chloride, IV, added to 1 L of fluid.
  - potassium <3.5 mmol/L: add 40 mmol (2 ampoules).
  - potassium 3.5–5.5 mmol/L: add 20 mmol (1 ampoule).
  - potassium >5.5 mmol/L: do not add any potassium.

  Maximum potassium dose: 40 mmol/hour.
  Monitor potassium hourly initially, then 2 hourly when stabilised.

LoE:III

If serum potassium results are not readily available:
- Potassium chloride, IV, 20 mmol (1 ampoule) added to 1 L of fluid as soon as **the patient has established adequate urinary output.**

Bicarbonate
There is no proven role for the use of intravenous sodium bicarbonate and it could potentially cause harm.

Insulin therapy
Patients should be preferentially managed with continuous intravenous infusions or hourly intramuscular injections (see below) in a high care ward, with appropriate monitoring.

Note:
» Ketonaemia takes longer to clear than hyperglycaemia and combined insulin and glucose (and K+) are needed to ensure clearance of ketonaemia.
» Avoid focusing on glucose control alone!
» Continue insulin until acidosis and ketosis have resolved.

Continuous intravenous infusion:
- Insulin, **short-acting,** IV infusion, 50 units in 200 mL sodium chloride 0.9%.
  - 4 mL solution = 1 unit insulin.
  - Initial infusion: 0.1 unit/kg/hour.
  - Usually 5–7 units/hour: 20–28 mL/hour.
  - If plasma glucose does not fall by 3 mmol/L in the 1st hour, double the insulin infusion (hourly) until a steady reduction of plasma glucose is achieved, i.e. at least 3–4 mmol/L per hour.
  - If plasma glucose <14 mmol/L, reduce insulin infusion rate to 1–2 units/hour and adjust subsequently according to hourly bedside capillary glucose level measured with glucose test strips.

Hourly intramuscular bolus injections:
Where intravenous infusion cannot be safely administered:
- Insulin, **short-acting**
  - Dilute 100 units with sodium chloride 0.9% to 10 mL i.e. 10 units/mL.
  - Loading dose: 0.5 units/kg body weight.
  - Administer half the dose as an intravenous bolus injection and the other half IM. Do not administer with an insulin syringe and needle.
  - Subsequent hourly doses: ± 5–10 units IM every hour (i.e. 0.1 units/kg/hour) and titrated against the bedside capillary glucose level.

Progress management
Continue insulin therapy until the acidosis has resolved and:
- the patient is able to eat, and
- subcutaneous insulin therapy is instituted either at previous doses or, for newly diagnosed diabetes at 0.5–1 unit/kg total daily dose divided into at least 2 doses with mixed short- and long-acting insulin (biphasic insulin $^2/_3$ in the morning and $^1/_3$ at night).

Infusion must overlap with subcutaneous regimen for 1–2 hour to avoid reversion to keto-acidosis.

Heparin.
For all patients**:**
- Low molecular weight heparin, e.g.:
- Enoxaparin, SC, 40 mg daily.

LoE:I[xxiii]

OR

- Unfractionated heparin, SC, 5 000 units 12 hourly.

8.7 COMPLICATIONS OF DIABETES

Macrovascular complications
Diabetic patients with a history of myocardial infarction, vascular bypass, stroke or transient ischemic attack, peripheral vascular disease, claudication, or angina need secondary prevention with aspirin and a statin – see Section 3.1: Ischaemic heart disease and atherosclerosis, prevention.

Hypertension
See Section 3.6: Hypertension.

Dyslipidaemia
See Section 8.8: Dyslipidaemia.

8.7.1 DIABETIC NEUROPATHIES

E10.4† / E11.4† + (G63.2*/G99.0*/G59.0*)

DESCRIPTION

Neuropathies are a common complication of diabetes. They play an important role in the morbidity and mortality suffered by people with diabetes.

There are three major categories:
» peripheral neuropathy,
» autonomic neuropathy, and
» acute onset neuropathies.

MEDICINE TREATMENT

Ensure appropriate glycaemic control.
Exclude or treat other contributory factors e.g.:
» alcohol excess,
» vitamin B_{12} deficiency, if suspected,
» uraemia, and
» HIV infection.

Pain
See Section 26.1.4: Management of neuropathic pain.

Gastroparesis

- Metoclopramide, oral, 10 mg 8 hourly, 30 minutes before meals.

If ineffective, consult a specialist.

8.7.2 DIABETIC KIDNEY DISEASE

E10.0/E11.2/E12.2/E13.2/E14.2 + (N18.1-5/N18.9)

See Section 7.1.1: Chronic Kidney Disease.

8.7.3 DIABETIC FOOT ULCERS

L97/L08.8 + (E10.5/E11.5/E12.5/E13.5/E14.5)

GENERAL MEASURES

Metabolic control.
Treat underlying comorbidity (e.g.: corns, alcohol misuse, ingrown toenails).
Relieve pressure: non-weight bearing is essential.
Smoking cessation is essential.

Deep (limb-threatening) infection
X-ray of affected limb.
Surgical drainage as soon as possible with removal of necrotic or poorly vascularised tissue, including infected bone – **refer urgently.**
Revascularisation, if necessary.

Local wound care
Frequent wound debridement with scalpel, e.g. once a week.
Frequent wound inspection.
Absorbent, non-adhesive, non-occlusive dressings.

Superficial ulcer with extensive infection
Debridement with removal of all necrotic tissue.

MEDICINE TREATMENT

Superficial ulcer with extensive infection

Antibiotic therapy
For polymicrobial infection:
Topical antibiotics are not indicated.

- Amoxicillin/clavulanic acid, oral, 875/125 mg 12 hourly for 10 days.
  - Longer course of therapy may be necessary.

Severe infection
- Amoxicillin/clavulanic acid, IV, 1.2 g 8 hourly.

Severe penicillin allergy (Z88.0)
- Clindamycin, oral, 150–450 mg 8 hourly.

AND
- Gentamicin, IV, 6 mg/kg daily (see Appendix II for guidance on prescribing).

REFERRAL
Arterial revascularisation procedures.

8.8 DYSLIPIDAEMIA
E78.0-9/E78.8-9

DESCRIPTION
Non-pharmacological therapy plays a vital role in the management of dyslipidaemia. Many patients with mild or moderate dyslipidaemia will be able to achieve optimum lipid levels with lifestyle modification alone and may not require lifelong lipid modifying therapy.

Accompanying modifiable risk factors for coronary artery disease (CAD) e.g. hypertension, smoking, diabetes, must be sought and treated.

Underlying causes of secondary dyslipidaemia, e.g. excess alcohol intake, hypothyroidism, should be identified and corrected.

The goal of treatment should be explained clearly to the patient and the risks of untreated dyslipidaemia should be emphasised.

GENERAL MEASURES
Lifestyle modification
Dietary strategies are effective.
» Replace saturated fats with unsaturated fats (mono-and polyunsaturated fats) without increasing calories from fats.
» Consume a diet high in fruits, vegetables, nuts and whole unrefined grains.
Smoking cessation.
Increase physical activity.
Maintain ideal body weight.

MEDICINE TREATMENT
Indication for medicine therapy
Cardiovascular
The main indication for lipid-modifying medication is to reduce the risk of a cardiovascular event. Medicine therapy should be considered when non-pharmacological means have failed to reduce the lipid levels to within the target range. When lipid-lowering medicines are used, this is **always** in conjunction with ongoing lifestyle modification.

Patients with any of the following factors are at a relatively high risk for a cardiovascular event and would benefit from lipid lowering therapy:
» established atherosclerotic disease
  - confirmed ischaemic heart disease
  - peripheral vascular disease
  - atherothrombotic stroke
» type 2 diabetics with age >40 years of age

» type 1 diabetes with microalbuminuria
» diabetes with chronic kidney disease (eGFR <60 mL/minute). LoE:I[xxiv]

Patients without established vascular disease, with a risk of MI ≥20% in 10 years: lifestyle modification and start statin treatment - see Section 3.1: Ischaemic heart disease and atherosclerosis, prevention.

Non-cardiovascular

The most serious non-cardiovascular complication of dyslipidaemia is the development of acute pancreatitis. This is seen in patients with severe hypertriglyceridaemia (fasting triglycerides >10 mmol/L). Ideally such patients should be discussed with a lipid specialist.

Fibrates are the medicines of choice for severe hypertriglyceridaemia not due to secondary causes.

Choice of medication

Depends on the type of lipid disturbance:

» predominant hypercholesterolaemia: statin
» mixed hyperlipidaemia: statin or fibrate
» predominant hypertriglyceridaemia: fibrate

- HMGCoA reductase inhibitors (statins), according to table below:

INDICATION	HMGCOA REDUCTASE INHIBITOR (STATIN) DOSE
A: Primary prevention - no existing CVD	
» Type 2 diabetes with age >40 years. » Diabetes for >10 years. » Diabetes with chronic kidney disease. » ≥20% 10-year risk of cardiovascular event.	▪ HMGCoA reductase inhibitors (statins), e.g.: • Simvastatin, oral, 10 mg at night.
» Patients on protease inhibitors. (Risks as above, after switching to atazanavir – see Section below).	• Atorvastatin, oral, 10 mg at night.
B: Secondary prevention – existing CVD	
» Ischaemic heart disease. » Atherothrombotic stroke. » Peripheral vascular disease.	▪ HMGCoA reductase inhibitors (statins), e.g.: • Simvastatin, oral, 40 mg at night LoE:I[xxv]
» Patients on protease inhibitors.	• Atorvastatin, oral, 10 mg at night. LoE:I[xxvi]
» Patients on amlodipine (and not on protease inhibitor).	• Simvastatin, oral, 10–20 mg at night. LoE:III[xxvii]

» If patient complains of muscle pain.	Reduce dose: ▪ HMGCoA reductase inhibitors (statins), e.g.: • Simvastatin, oral, 10 mg at night. **OR** Consult specialist for further management. *LoE:III*[xxviii]

Note: Lipid-lowering medicines must always be used in conjunction with ongoing lifestyle modification.

For patients with moderate to severe fasting hypertriglyceridaemia and for patients on antiretroviral therapy i.e. triglycerides >10 mmol/L:

- ▪ Fibrates, e.g.:
- • Bezafibrate, slow release, oral, 400 mg daily.

Aspirin therapy:

Use in adult patients with diabetes who have a history of cardiovascular disease i.e.

- ischaemic heart disease
- peripheral vascular disease
- previous thrombotic stroke

- • Aspirin, oral, 150 mg daily. *LoE:I*[xxix]

Dyslipidaemia in HIV-infected patients: See Section 10.1.2: Management of selected antiretroviral adverse drug reactions.

REFERRAL

» Patients with possible familial hypercholesterolaemia (FH) i.e. random cholesterol >7.5 mmol/L or with tendon xanthomata (See Section 3.1: Ischaemic heart disease and atherosclerosis).
» Suspected severe familial dyslipidaemias.

8.9 HYPERCALCAEMIA, INCLUDING PRIMARY HYPERPARATHYROIDISM

E83.5 + (E21.0/D71)

DESCRIPTION

When serum calcium (corrected for albumin) concentrations exceed the upper limit of normal.

Aetiology

» Ambulatory patients: most common cause is hyperparathyroidism (>90% of cases).
» Hospitalised patients: malignancies are the most common cause (65% of cases). Hyperparathyroidism accounts for another 25%.
» Granulomatous disease (e.g. sarcoid).

» Immobilisation in those with high bone turnover.

Investigations
Draw blood for parathyroid hormone (PTH) and simultaneous calcium, phosphate, magnesium, albumin, creatinine and sodium and potassium, and 25 hydroxy-vitamin D concentrations.
A detectable PTH in the presence of hypercalcaemia indicates PTH-dependent hyperparathyroidism.

MEDICINE TREATMENT
Hypercalcaemia
Patients with moderate/severe hypercalcaemia should be kept well hydrated and may need several litres of fluid.

Avoid thiazide diuretics in the acute setting as they increase serum calcium concentration.

The addition of furosemide has not been shown to be of benefit.

For symptomatic hypercalcaemia:
- Sodium chloride solution 0.9%, IV infusion, 4–6 L in 24 hours.
  - Monitor urine output.

If still symptomatic after 24 hours and adequate hydration, **or** if initial serum calcium is >3 mmol/L:
ADD
- Bisphosphonates, e.g.:
- Zoledronic acid, IV infusion, 4 mg over 15 minutes (specialist initiated).
  - eGFR 35 to 60 mL/minute, adjust dose in consultation with specialist.
  - **Note**: Do not use if eGFR <35 mL/minute. *LoE:I*[xxx]

In patients with granulomatous disease and haematological malignancies:
- Corticosteroids (intermediate-acting) e.g.:
- Prednisone, oral, 40 mg depending on response, daily.

LoE:III[xxxi]

REFERRAL
When a diagnosis of hyperparathyroidism is confirmed or other cause is not obvious.

8.10 HYPOCALCAEMIA
E83.5 + (E20.0-1/E20.8-9)

DESCRIPTION
Serum calcium (corrected for albumin) below the lower limit of normal.
Causes
» Renal failure.
» Hypoparathyroidism:

  - post neck surgery,
  - radiotherapy, or
  - idiopathic.
» Vitamin D-related, (deficient intake, activation or action).
» Hypomagnesaemia.
» Malabsorption syndrome.

MEDICINE TREATMENT
Therapy is aimed at treating the underlying cause.

For acute hypocalcaemia with neurological problems and prolonged QT time on ECG:

- Calcium gluconate 10%, infusion, 20 mL in 100 mL dextrose 5% given over 20 minutes, with ECG monitoring.

AND

- Calcium gluconate 10%, infusion, 15 mg/kg (= wt [kg] x 1.7 mL) in 1000 mL sodium chloride 0.9% over 4 hours.

LoE:III[xxxii]

For hypoparathyroidism:

- Alfacalcidol, oral, 1–3 mcg daily.

AND

- Calcium, elemental, oral, 500–1 500 mg daily in divided doses.

Correct magnesium deficiency if present.

Renal failure:
See Section: 7.1.1 Chronic Kidney Disease (CKD).

REFERRAL
» If cause is uncertain.
» If hypoparathyroidism suspected and PTH analysis required as above.

8.11 HYPOTHYROIDISM
E03.0-5/E03.8-9

DESCRIPTION
Causes
Common causes of primary hypothyroidism are:
» chronic autoimmune thyroiditis,
» post-surgery, and
» post radio-active iodine.
Secondary hypothyroidism (less than 1% of cases) may be due to any cause of anterior hypopituitarism.

Investigations
Thyroid stimulating hormone (TSH) and thyroxine (T_4) initially. In primary hypothyroidism TSH is elevated and T_4 is low. If TSH is normal or slightly elevated and T_4 is low this suggests hypopituitarism: take blood for cortisol and ACTH, give hydrocortisone replacement before starting levothyroxine and investigate for causes of hypopituitarism.

MEDICINE TREATMENT

- Levothyroxine, oral, 100 mcg daily.
  - If there is a risk of ischaemic heart disease, start at 25 mcg daily and increase by 25 mcg every 4 weeks.

Check TSH and T_4 after 2–3 months and adjust dose if required.
TSH levels will take several weeks to stabilise. Once stable check T_4 and TSH annually.

Hypothyroidism in pregnancy
About 60% of hypothyroid pregnant women need an increase in levothyroxine therapy in the second and third trimesters. Because T_4 takes a long time to reach steady state and 1st trimester hypothyroidism is undesirable for the fetus, for patients with borderline control (TSH>1.2mU/L) it is advisable to increase the pre-pregnancy dose by 30%. Check TSH monthly and increase levothyroxine doses to keep serum TSH levels low normal and free T_4 levels in the high-normal range. After delivery, revert to pre-conception doses.
Note: TSH and T_4 reference range is trimester-specific.

LoE:II[xxxiii]

8.12 OSTEOPOROSIS

M80.00-59/M80.80-99/M81.00-69/M81.80-99/M82.00-19/M82.80-89

DESCRIPTION

A disease characterised by low bone mass and micro-architectural bone deterioration leading to bone fragility and increase in fracture risk.

GENERAL MEASURES

Prevention
Adequate energy and protein intake.
Adequate dietary calcium intake (>1 g/day) particularly in the young, in breastfeeding mothers and in the elderly. This is preferably obtained from a dietary source.
Weight bearing exercises, e.g. brisk 30-minute walk 3 times a week.
Smoking cessation.
Avoid excessive alcohol intake - >2 units daily has a 40% increased risk of sustaining any osteoporotic fracture, compared to people with moderate or no alcohol intake.
Avoid falls.

LoE:III[xxxiv]

MEDICINE TREATMENT

Primary prevention

In institutionalised frail elderly patients, supplementation with calcium and vitamin D may reduce the incidence of hip fractures:

- Calcium, elemental, oral, 1 000 mg daily.

AND

- Vitamin D (Calciferol), oral, 800 units daily **or** 50 000 of Calciferol every 4 weeks. *LoE:III*[xxxv]

Note: Routine supplementation with calcium and vitamin D marginally increases the risk of myocardial infarction and stroke and is of unclear benefit in other populations. *LoE:I*[xxxvi]

Secondary prevention

Secondary prevention of osteoporotic fracture, including patients on long-term corticosteroids:

In severe osteoporosis, i.e. patients who have a T-score of –2.5 (severe osteoporosis) plus an osteoporotic fracture:

- Bisphosphonates, e.g.:
- Alendronic acid, oral, 70 mg weekly, for a maximum duration of 5 years.
  - Taken with a full glass of water, 30 minutes before breakfast – do not lie down.

LoE:I[xxxvii]

Supplement with:

- Calcium, elemental, oral, 1 000mg daily.

AND

- Vitamin D (Calciferol), oral, 800 units daily.

Hormone replacement therapy

See Section 5.12: Menopause and Perimenopausal Syndrome.
Only indicated early in menopause, if vasomotor symptoms are significant.
Review contra-indications before initiating therapy.

REFERRAL

» To establish diagnosis (bone densitometry).
» For initial assessment.
» Initiation of, and monitoring response to, therapy, and 18–24 monthly bone mineral density (BMD).
» Fractures suspected to be due to osteoporosis for consideration for alendronate.
» Patients not tolerating oral bisphosphonate.
» Patients with e-GFR < 30 mL/minute.

8.13 OSTEOMALACIA/RICKETS

M83.00-59/M83.80-99/E55.0

DESCRIPTION

A disorder of mineralisation of newly synthesised bone matrix.

REFERRAL

All patients.

8.14 PAGET'S DISEASE

M88.08/M88.80-99

DESCRIPTION

Bone disease characterised by localised uncontrolled formation of highly active osteoclasts leading to an increase in bone resorption followed by chaotic increase in bone formation.

GENERAL MEASURES

Most cases are mild and asymptomatic and no treatment is required. The diagnosis is supported by isolated high alkaline phosphatase and typical CXR radiological changes.

Avoid high calcium diet when immobile as hypercalcaemia may occur with immobilisation.

Differentiate bone pain of Paget's, especially at night, from arthritic pain in joints near deformed bone, e.g. hip and knee joints, as well as pain resulting from fracture or complicating osteosarcoma.

MEDICINE TREATMENT

For arthritic pain:

- NSAID, e.g.:
- Ibuprofen, oral, 400 mg 8 hourly with meals.

REFERRAL

All patients.

8.15 PITUITARY DISORDERS

Includes prolactinoma, anterior hypothyroid hypopituitarism and diabetes insipidus.

8.15.1 PROLACTINOMA

D35.2 + (M8271/0)

DESCRIPTION

Prolactinoma is the most common functioning pituitary tumour.

Investigations
Serum prolactin, β-hCG.

Note:
» There are numerous causes of hyperprolactinaemia other than a prolactinoma, so secondary causes must be excluded e.g. pregnancy, medicines, physiological, hypothyroidism, chronic renal failure and tumours.
» In patients with prolactinoma, serum prolactin levels are usually elevated ≥4 times the upper limit of the normal reference range for the laboratory method used. Lesser degree of elevation of serum prolactin may also be found in patients with other pituitary tumours associated with pituitary stalk compression.

MEDICINE TREATMENT
Dopamine agonist therapy is the treatment of choice.
- Bromocriptine, oral, 1.25 mg at bedtime with a snack.
  - Initial maintenance dose: increase dose to 2.5 mg 12 hourly with food and check prolactin 4 weeks later.
  - Higher doses may be needed.
  - GIT side effects are minimised by giving doses with food.
  - If total dose of 10 mg does not normalise prolactin, refer.

REFERRAL
» All tumours, once causes of secondary hyperprolactinaemia have been sought and excluded.
» Intolerance to bromocriptine.
» Unexplained hyperprolactinemia.

Urgent
» Any visual disturbances, **especially those** suggesting compression of optic chiasm.
» Pituitary apoplexy.

8.15.2 ANTERIOR HYPOPITUITARISM
E23.0-3/E28.3/E29.1

DESCRIPTION
Absent or diminished secretion of one or more anterior pituitary hormones due to primary damage of the anterior pituitary gland, or secondary to hypothalamic dysfunction, which may result in hypothyroidism and/or hypoadrenalism and/or hypogonadism or growth retardation in children.

GENERAL MEASURES
Surgery is required for large tumours, pituitary apoplexy, and hormone secreting tumours (except for most patients with prolactinomas, who generally

respond well to medical therapy).
Radiotherapy may be required in selected patients.
A notification bracelet is needed.

MEDICINE TREATMENT

Acute crisis
Treat as for acute crisis in Section 8.2: Adrenal Insufficiency (Addison's Disease).

Chronic
See Section 8.2: Adrenal Insufficiency (Addison's Disease).

Hypoadrenalism
See Section 8.2: Adrenal Insufficiency (Addison's disease) and 8.11: Hypothyroidism.

Hypothyroidism
See Section 8.11: Hypothyroidism.

Hypogonadism
Individualise dosage and need for replacement according to age, symptoms, etc.

Women:
As for postmenopausal HT, see Section 5.12: Menopause and perimenopausal syndrome.

Men:
- Testosterone cypionate, IM, 200–300 mg every 3–4 weeks.

See Section 8.3: Androgen deficiency.

REFERRAL

All diagnosed patients for initial assessment.

8.15.3 DIABETES INSIPIDUS (POSTERIOR HYPOPITUITARISM)

E23.2

DESCRIPTION

Damage to the posterior pituitary leading to deficient production of antidiuretic hormone. Characterised by the passage of large amounts of dilute urine, usually >2.5 litres daily.
Causes include head trauma and neurosurgery but most cases are idiopathic.
Consultation with a specialist is recommended.

GENERAL MEASURES

Rehydration with water or hypotonic fluids.

MEDICINE TREATMENT

Postoperative or acutely ill patients:

- Desmopressin, IV/SC, 2–4 mcg daily, either as a single dose or in 2 divided doses.

OR

- Desmopressin, nasal spray, 10–40 mcg daily, either as a single dose or in 2–3 divided doses.

OR

- Desmopressin, oral, 0.05 mg, 8–12 hourly.
  - Optimal dose: 0.1–0.8 mg daily.
  - Adjust dose according to response to a maximum of 1.2 mg daily in divided doses.

If patient has a normal thirst mechanism, and does not receive IV fluids for other purposes:

» oral, intranasal, or IV/SC dosing can be used; and
» keep urine osmolality at 450–600 mOsm/kg.

If patient requires IV fluids and/or is unable to regulate total fluid intake by thirst mechanism:

» IV dosing is preferred; and
» continually adjust the level of antidiuresis to maintain hydration and plasma sodium within the normal.

Replacement therapy:

- Desmopressin, nasal spray, 10–40 mcg daily, either as a single dose or in 2–3 divided doses.
  - Adjust morning and evening doses separately for appropriate diurnal rhythm of water turnover.

OR

- Desmopressin, oral, 0.05 mg, either as a single dose or in 2–3 divided doses.
  - Optimal dose: 0.1–0.8 mg daily.
  - Adjust dose according to response to a maximum of 1.2 mg daily in divided doses.

LoE:III[xxxviii]

REFERRAL

All patients diagnosed or suspected.

Water deprivation may be necessary to confirm the diagnosis. Careful monitoring of electrolytes and exclusion of fluid overload while on therapy is essential to determine the appropriate dose.

8.16 PHAEOCHROMOCYTOMA

C74.0-1/C74.9/C79.7/D09.3/D35.0/D44.1 + (M8700/0/3/6)

Description

Catecholamine-secreting tumour of the adrenal medulla.

Clinical presentation

Always consider in hypertensive patients who have paroxysmal symptoms:

- » headaches,
- » GIT symptoms,
- » palpitations,
- » anxiety.
- » tremor,
- » recurrent chest discomfort,
- » sweating, and

There is marked inter-individual variation in symptoms.
Patients may also have orthostatic changes in BP.

Diagnosis

24-hour urine acidified with HCl: normetanephrine (NMA), vanillylmandelic acid (VMA), should be ≥ twice normal for a definite diagnosis. Test is best done during a paroxysm, if possible, using at least 2 samples.
There are many drugs, foods and diseases that can falsely elevate or lower NMA/VMA levels; therefore, the clinician must interpret the results in the light of the clinical context and after having taken an accurate history.

Screen:

- » young hypertensive patients;
- » hypertensive patients with paroxysmal symptoms; and
- » patients with:
  - — The classic triad of headache, sweating, and tachycardia, whether or not they have hypertension
  - — a family history of a phaeochromocytoma,
  - — A familial syndrome that predisposes to catecholamine-secreting tumours (e.g., multiple endocrine neoplasia type 2 [MEN2], neurofibromatosis type 1 [NF1], or von Hippel-Lindau [VHL]). or
  - — radiologic evidence of an adrenal mass (adrenal incidentaloma) with or without hypertension.

GENERAL MEASURES

Surgical removal of the tumour.

MEDICINE TREATMENT

Once diagnosis is confirmed, initiate medication with immediate referral.

- Alpha blockers, e.g.:
- Doxazosin, oral, 4 mg daily.
  - Dose increase above 8 mg daily to control blood pressure may be required.

LoE:III[xxxix]

- Calcium channel blockers may be added, e.g.:

- Amlodipine, oral, 5–10 mg daily.

Note:
» Do not give patients diuretic therapy unless pulmonary oedema is present.
» β-blockers must be used with extreme caution in the management of phaeochromocytoma, and only after adequate alpha blockade.

LoE:III[xi]

REFERRAL
All patients.

8.17 PRIMARY ALDOSTERONISM
E26.0

DESCRIPTION
Increased aldosterone production usually due to an adrenal adenoma (Conn's syndrome) or idiopathic bilateral adrenal hyperplasia (the majority of cases).

Clinical
Suspect in a patient with resistant hypertension or hypertension with hypokalaemia.

Diagnosis
Elevated serum aldosterone with a suppressed renin level **and** elevated aldosterone/renin ratio.
ACE-inhibitors, angiotensin receptor blockers (ARBs), and diuretics can give falsely elevated or lowered results. Stop all these drugs for a minimum of 2 weeks before testing. Stop spironolactone for 6 weeks before testing.

Because of limited specificity, a positive screening test result should be followed by a confirmatory test. A negative random ratio test does not necessarily exclude the diagnosis.

MEDICINE TREATMENT
Adrenal adenoma
A surgical reSection/removal of adenoma.

Bilateral hyperplasia
Standard anti-hypertensive therapy, including spironolactone.
- Spironolactone, oral, 100–200 mg daily.

REFERRAL
All patients to an endocrinologist or a hypertension centre for confirmation of the diagnosis and further treatment.

8.18 HYPERTHYROIDISM

E05.0-5/E05.8-9

DESCRIPTION

Most common cause of hyperthyroidism is Graves' disease, which is an autoimmune condition resulting from the presence of thyroid stimulating autoantibodies. Other common causes are toxic single or multinodular goitre and sub-acute thyroiditis. Thyrotoxicosis in the setting of any other acute life-threatening condition such as cardiac failure etc. should be managed as thyroid crisis – see Section 8.18.5: Thyroid crisis.

Investigation

TSH and free T_4.
If TSH suppressed and free T_4 normal, request free T_3.
The usual biochemical abnormalities are: low TSH, elevated free $T_{4/3}$.
TSH receptor antibodies should be measured in all patients.

Once thyrotoxicosis is confirmed, if cause is uncertain request thyroid uptake scan. If uptake is:

» Elevated or diffuse: Grave's disease.
» Markedly decreased: Thyroiditis.
» Patchy uptake with areas of increased uptake: Toxic multinodular goitre.

REFERRAL

» Consultation with a specialist is recommended in all cases.
» For thyroid scan if necessary.
» Thyroid-associated ophthalmopathy.
» When radioactive iodine or surgery is contemplated.
» If patient is pregnant.

8.18.1 GRAVES' HYPERTHYROIDISM

E05.0

MEDICINE TREATMENT

- Carbimazole, oral, 20–40 mg daily.
  - Titrate dose according to thyroid hormone levels (T_4).
  - Duration of therapy: 12–18 months.
  - Durations of therapy longer than 12 months must be in consultation with a specialist.

ß–blockers

» Used to counteract excessive sympathetic symptoms, e.g. palpitations.
» Dose is titrated according to the heart rate.
» Give for 2–6 weeks, together with carbimazole until T4 levels normalise.

- ß–blocker, e.g.:
- Atenolol, oral, 50 mg daily.

- Titrate according to symptom control up to 100 mg daily. LoE:III[xli]

Radioactive iodine
In the setting of Graves' disease radioactive iodine may be administered for failed medical therapy and may be indicated for patients with coexistent heart disease. Refer patient if radioactive treatment is contemplated.

Surgery
Seldom indicated, but to consider in the following situations: large thyroid causing obstructive symptoms, failure of anti-thyroid medicine therapy, allergy to anti-thyroid therapy, 2nd trimester of pregnancy, and not responding to or allergic to anti-thyroid medication.

Monitoring
Patients with Graves' disease who are treated with anti-thyroid drugs should be monitored every 6–8 weeks using a serum T_4. TSH may remain suppressed for months. Once in remission, patients may be monitored less frequently to determine signs and symptoms of recrudescence of thyrotoxicosis.

Because there is a risk of neutropenia or agranulocytosis with carbimazole, therapy should be temporarily stopped and a white cell count (with differential) must be done in patients presenting with an infection or sore throat.

Post-radio-active iodine TSH and free T_4 should be checked at 6 weeks, 3, 6, 9 and 12 months and annually thereafter until either hypothyroidism occurs or patient remains euthyroid for ± 3–4 years. Although uncommon, new onset hypothyroidism can occur years later.

8.18.2 TOXIC MULTINODULAR GOITER
E05.2

MEDICINE TREATMENT
Radio-active iodine
Radioactive iodine is the treatment of choice. Medical therapy is indicated initially for patients with underlying heart disease to achieve euthyroidism before radio-active iodine. Surgery is restricted to patients with obstructive symptoms.

8.18.3 SINGLE TOXIC NODULES
E05.1

MEDICINE TREATMENT
Radioactive iodine
Smaller nodules are best managed with radio-active iodine while larger nodules may require surgery.

ß–blockers
» Used to counteract excessive sympathetic symptoms, e.g. palpitations.
» Dose is titrated according to the heart rate.
» Give for 2–4 weeks.

- ß–blocker, e.g.:
- Atenolol, oral, 50 mg daily.
  - Titrate according to symptom control up to 100 mg daily.

8.18.4 THYROIDITIS

E06.0-5/E06.9

Toxic phase lasts up to 3 months.

MEDICINE TREATMENT

ß–blockers

Used to counteract excessive sympathetic symptoms, e.g. palpitations.
Dose is titrated according to the heart rate.
Give for 2–4 weeks.

- ß–blocker, e.g.:
- Atenolol, oral, 50 mg daily
  - Titrate according to symptom control up to 100 mg daily.

For painful subacute thyroiditis (De Quervain's): E06.1

- NSAID, e.g.:
- Ibuprofen, oral, 400 mg 8 hourly with meals.

AND

- Corticosteroids (intermediate-acting) e.g.:
- Prednisone, oral, 40 mg daily (Specialist consultation). *LoE:III*[xlii]

8.18.5 THYROID CRISIS

E05.5

MEDICINE TREATMENT

IV fluids as indicated.

- Carbimazole, oral, 40–60 mg 6 hourly until crisis is controlled.

30 minutes after the first dose of carbimazole: *LoE:III*[xliii]

- Lugol's iodine, oral, 10 drops in milk, 8 hourly.

AND

- ß–blocker, e.g.:
- Atenolol, oral, 50 mg daily
  - Titrate according to symptom control up to 100 mg daily.

If life-threatening:

ADD

- Hydrocortisone, IV, 100 mg 8 hourly.

Actively manage precipitating illness and infection. ICU admission is desirable.

REFFERRAL

All patients once stabilised.

References:

[i] ACTH, IM: South African Medicines Formulary. 12th Edition. Division of Clinical Pharmacology.University of Cape Town. 2016.

[ii]Hydrocortisone, IV: Bornstein SR, Allolio B, Arlt W, Barthel A, Don-Wauchope A, Hammer GD, Husebye ES, Merke DP, Murad MH, Stratakis CA, Torpy DJ. Diagnosis and Treatment of Primary Adrenal Insufficiency: An Endocrine Society Clinical Practice Guideline. J Clin Endocrinol Metab. 2016 Feb;101(2):364-89. https://www.ncbi.nlm.nih.gov/pubmed/26760044

[iii] Sodium chloride 0.9%, IV: The Society for Endocrinology, Metabolism and Diabetes of South Africa Type 2 Diabetes Guidelines Expert Committee. The 2017 SEMDSA Guideline for the Management of Type 2 Diabetes Guideline Committee. JEMDSA 2017; 21(1)(Supplement 1): S1-S196. http://www.jemdsa.co.za/index.php/JEMDSA/article/view/647/937

Dextrose 50%, IV: The Society for Endocrinology, Metabolism and Diabetes of South Africa Type 2 Diabetes Guidelines Expert Committee. The 2017 SEMDSA Guideline for the Management of Type 2 Diabetes Guideline Committee. JEMDSA 2017; 21(1)(Supplement 1): S1-S196. http://www.jemdsa.co.za/index.php/JEMDSA/article/view/647/937

Sodium chloride 0.9%/ dextrose 5%, IV: The Society for Endocrinology, Metabolism and Diabetes of South Africa Type 2 Diabetes Guidelines Expert Committee. The 2017 SEMDSA Guideline for the Management of Type 2 Diabetes Guideline Committee. JEMDSA 2017; 21(1)(Supplement 1): S1-S196. http://www.jemdsa.co.za/index.php/JEMDSA/article/view/647/937

[iv] Corticosteroids, oral (intermediate-acting therapeutic class): South African Medicines Formulary. 12th Edition. Division of Clinical Pharmacology.University of Cape Town. 2016.

[v] Fludrocortisone, oral: The Society for Endocrinology, Metabolism and Diabetes of South Africa Type 2 Diabetes Guidelines Expert Committee. The 2017 SEMDSA Guideline for the Management of Type 2 Diabetes Guideline Committee. JEMDSA 2017; 21(1)(Supplement 1): S1-S196. http://www.jemdsa.co.za/index.php/JEMDSA/article/view/647/937

[vi]Hydrocortisone, IV: Bornstein SR, Allolio B, Arlt W, Barthel A, Don-Wauchope A, Hammer GD, Husebye ES, Merke DP, Murad MH, Stratakis CA, Torpy DJ. Diagnosis and Treatment of Primary Adrenal Insufficiency: An Endocrine Society Clinical Practice Guideline. J Clin Endocrinol Metab. 2016 Feb;101(2):364-89. https://www.ncbi.nlm.nih.gov/pubmed/26760044

[vii] Testosterone cypionate, IM: Fernández-Balsells MM, Murad MH, Lane M, Lampropulos JF, Albuquerque F, Mullan RJ, Agrwal N, Elamin MB, Gallegos-Orozco JF, Wang AT, Erwin PJ, Bhasin S, Montori VM. Clinical review 1: Adverse effects of testosterone therapy in adult men: a systematic review and meta-analysis. J Clin Endocrinol Metab. 2010 Jun;95(6):2560-75. https://www.ncbi.nlm.nih.gov/pubmed/20525906

Testosterone cypionate, IM: Pfizer, MCC registered package insert: Depo-testosterone™, 31 January 2016.

[viii] Dexamethasone, oral: Findling JW, Raff H, Aron DC. The low-dose dexamethasone suppression test: a reevaluation in patients with Cushing's syndrome. J Clin Endocrinol Metab. 2004 Mar;89(3):1222-6. http://www.ncbi.nlm.nih.gov/pubmed/15001614

[ix] Diagnosis of diabetes mellitus: The Society for Endocrinology, Metabolism and Diabetes of South Africa Type 2 Diabetes Guidelines Expert Committee. The 2017 SEMDSA Guideline for the Management of Type 2 Diabetes Guideline Committee. JEMDSA 2017; 21(1)(Supplement 1): S1-S196. http://www.jemdsa.co.za/index.php/JEMDSA/article/view/647/937

Diagnosis of diabetes mellitus: National Department of Health: Affordable Medicines, EDP-Adult Hospital level. Review: HbA1c as a diagnostic test for diabetes, October 2017. http://www.health.gov.za/

Diagnosis of diabetes mellitus: Wheeler E, Leong A, Liu CT, et al. Impact of common genetic determinants of Hemoglobin A1c on type 2 diabetes risk and diagnosis in ancestrally diverse populations: A transethnic genome-wide meta-analysis. PLoS Med. 2017 Sep 12;14(9):e1002383. https://www.ncbi.nlm.nih.gov/pubmed/28898252

Diagnosis of diabetes mellitus: Herman WH, Ma Y, Uwaifo G, et al. Diabetes Prevention Program Research Group. Differences in A1C by race and ethnicity among patients with impaired glucose tolerance in the Diabetes Prevention Program. Diabetes Care 2007;30:2453–2457. https://www.ncbi.nlm.nih.gov/pubmed/17536077

[x] Monitoring of diabetes mellitus: The Society for Endocrinology, Metabolism and Diabetes of South Africa Type 2 Diabetes Guidelines Expert Committee. The 2017 SEMDSA Guideline for the Management of Type 2 Diabetes Guideline Committee. JEMDSA 2017; 21(1)(Supplement 1): S1-S196. http://www.jemdsa.co.za/index.php/JEMDSA/article/view/647/937

[xi] Urine protein monitoring by dipstix: McFarlane P. Gilbert RE, MacCallum L, Senior P. Chronic Kidney Disease in Diabetes. Can J Diabetes 37 (2013) S129eS136.

Urine protein monitoring by dipstix: The Society for Endocrinology, Metabolism and Diabetes of South Africa Type 2 Diabetes Guidelines Expert Committee. The 2017 SEMDSA Guideline for the Management of Type 2 Diabetes Guideline Committee. JEMDSA 2017; 21(1)(Supplement 1): S1-S196. http://www.jemdsa.co.za/index.php/JEMDSA/article/view/647/937

Urine protein monitoring by dipstix: Noubiap JJ, Naidoo J, Kengne AP. Diabetic nephropathy in Africa: A systematic review. World J Diabetes. 2015 Jun 10;6(5):759-73. https://www.ncbi.nlm.nih.gov/pubmed/26069725

Urine protein monitoring by dipstix: MR Davids, N Marais, JC Jacobs. South African Renal Registry. Annual Report 2012. South African Renal Society, Cape Town 2014. http://sa-renalsociety.org/registry/

[xii] Metformin: Effect of intensive blood-glucose control with metformin on complications inoverweight patients with type 2 diabetes (UKPDS 34). UK Prospective Diabetes Study (UKPDS) Group.Lancet. 1998 Sep

12;352(9131):854-65. Erratum in: Lancet1998 Nov 7;352(9139):1558.http://www.ncbi.nlm.nih.gov/pubmed/9742977

Metformin: South African Medicines Formulary. 12th Edition. Division of Clinical Pharmacology.University of Cape Town. 2016.

[xiii] Metformin (renal impairment): Canadian Diabetes Association Clinical Practice Guidelines Expert Committee. Canadian Diabetes Association 2013 Clinical Practice Guidelines for the Prevention and Management of Diabetes in Canada. Can J Diabetes 2013;37(suppl 1):S1-S212.
http://guidelines.diabetes.ca/app_themes/cdacpg/resources/cpg_2013_full_en.pdf

Metformin (renal impairment): The National Institute for Health and Care Excellence. Type 2 diabetes in adults: management Clinical Guideline, 2 December 2015. https://www.nice.org.uk/guidance/ng28

Metformin (renal impairment): Aronoff, Bennett et al. Drug Prescribing in Renal Failure: Dosing Guidelines for Adults and Children, 5th Edition. American College of Physicians.United States of America, 2007.

Metformin (renal impairment): Lipska KJ, Bailey CJ, Inzucchi SE. Use of metformin in the setting of mild-to moderate renal insufficiency. Diabetes Care. 2011 Jun;34(6):1431-7.
http://www.ncbi.nlm.nih.gov/pubmed/21617112

Metformin (renal impairment): South African Medicines Formulary. 12th Edition. Division of Clinical Pharmacology.University of Cape Town. 2016.

[xiv] Glimepiride: South African Medicines Formulary. 12th Edition. Division of Clinical Pharmacology. University of Cape Town. 2016.

[xv] Sulfonylureas: Niemi M, Backman JT, Neuvonen M, Neuvonen PJ, Kivistö KT. Effects of rifampin on the pharmacokinetics and pharmacodynamics of glyburide and glipizide. Clin Pharmacol Ther. 2001 Jun;69(6):400-6. https://www.ncbi.nlm.nih.gov/pubmed/11406737

[xvi] Insulin, biphasic, SC (starting dose): The Society for Endocrinology, Metabolism and Diabetes of South Africa Type 2 Diabetes Guidelines Expert Committee. The 2017 SEMDSA Guideline for the Management of Type 2 Diabetes Guideline Committee. JEMDSA 2017; 21(1)(Supplement 1): S1-S196.
http://www.jemdsa.co.za/index.php/JEMDSA/article/view/647/937

[xvii] Insulin therapy (Type 2 diabetes mellitus): The Society for Endocrinology, Metabolism and Diabetes of South Africa Type 2 Diabetes Guidelines Expert Committee. The 2017 SEMDSA Guideline for the Management of Type 2 Diabetes Guideline Committee. JEMDSA 2017; 21(1)(Supplement 1): S1-S196.
http://www.jemdsa.co.za/index.php/JEMDSA/article/view/647/937

[xviii] ACE-inhibitor:ACEI (ACE Inhibitors in Diabetic Nephropathy Trialist Group). Should all patients with type 1 diabetes mellitus and microalbuminuria receive angiotensin converting enzyme inhibitors? A meta-analysis of individual patient data. Annals of Internal Medicine 2001;134(5): 370–379.
http://www.ncbi.nlm.nih.gov/pubmed/11242497

[xix] Enalapril, oral (maximum daily dose of 40 mg): Joint Formulary Committee. British National Formulary. London: BMJ Group and Pharmaceutical Press; 2018.

[xx] Home blood glucose monitoring:Gerstein HC, Miller ME, Byington RP, Goff DC, Bigger JT, Buse JB, Cushman WC, Genuth S, Ismail-Beigi F, Grimm RH. et al. Effects of intensive glucose lowering in type 2 diabetes. N Engl J Med.2008;358(24):2545–2559.http://www.ncbi.nlm.nih.gov/pubmed/18539917

Home blood glucose monitoring:Östgren CJ, Sundström J, Svennblad B, Lohm L, Nilsson PM, Johansson G. Associations of HbA1c and educational level with risk of cardiovascular events in 32,871 drug-treated patients with Type 2 diabetes: a cohort study in primary care. Diabet Med. 2013 May;30(5):e170-7.
http://www.ncbi.nlm.nih.gov/pubmed/23350893

[xxi] Dextrose 50%, IV: Moore C, Woollard M. Dextrose 10% or 50% in the treatment of hypoglycaemia out of hospital? A randomised controlled trial. Emerg Med J. 2005 Jul;22(7):512-5.
https://www.ncbi.nlm.nih.gov/pubmed/15983093

Dextrose 50%, IV: The Society for Endocrinology, Metabolism and Diabetes of South Africa Type 2 Diabetes Guidelines Expert Committee. The 2017 SEMDSA Guideline for the Management of Type 2 Diabetes Guideline Committee. JEMDSA 2017; 21(1)(Supplement 1): S1-S196.
http://www.jemdsa.co.za/index.php/JEMDSA/article/view/647/937

[xxii] Dextrose 5%, IV: The Society for Endocrinology, Metabolism and Diabetes of South Africa Type 2 Diabetes Guidelines Expert Committee. The 2017 SEMDSA Guideline for the Management of Type 2 Diabetes Guideline Committee. JEMDSA 2017; 21(1)(Supplement 1): S1-S196.
http://www.jemdsa.co.za/index.php/JEMDSA/article/view/647/937

Dextrose 5% in sodium chloride 0.9%, IV: The Society for Endocrinology, Metabolism and Diabetes of South Africa Type 2 Diabetes Guidelines Expert Committee. The 2017 SEMDSA Guideline for the Management of Type 2 Diabetes Guideline Committee. JEMDSA 2017; 21(1)(Supplement 1): S1-S196.
http://www.jemdsa.co.za/index.php/JEMDSA/article/view/647/937

[xxiii]Enoxaparin: Wein L, Wein S, Haas SJ, Shaw J, Krum H. Pharmacological venous thromboembolism prophylaxis in hospitalized medical patients: a meta-analysis of randomized controlled trials. Arch Intern Med. 2007 Jul 23;167(14):1476-86. http://www.ncbi.nlm.nih.gov/pubmed/17646601

[xxiv]HMGCoA reductase inhibitor (indications - CKD, albuminuria): Hou W, Lv J, Perkovic V, Yang L, Zhao N, Jardine MJ, Cass A, Zhang H, Wang H. Effect of statin therapy on cardiovascular and renal outcomes in patients with chronic kidney disease: a systematic review and meta-analysis. Eur Heart J. 2013 Jun;34(24):1807-17. https://www.ncbi.nlm.nih.gov/pubmed/23470492

HMGCoA reductase inhibitor (indications - CKD, albuminuria): Qin X, Dong H, Fang K, Lu F. The effect of statins on renal outcomes in patients with diabetic kidney disease: A systematic review and meta-analysis. Diabetes Metab Res Rev. 2017 Sep;33(6). https://www.ncbi.nlm.nih.gov/pubmed/28477396

[xxv] Simvastatin 40 mg, oral (secondary prevention of ischaemic events): National Department of Health. Affordable Medicines, EDP-Primary Health Care. Cost-effectiveness analysis of high, intermediate, and low dose statins for the secondary prevention of cardiovascular disease, 31 January 2018. www.health.gov.za/

Simvastatin 40 mg, oral (secondary prevention of ischaemic events): Cholesterol Treatment Trialists' (CTT) Collaboration. Efficacy and safety of more intensive lowering of LDL cholesterol: a meta-analysis of data from 170 000 participants in 26 randomised trials. The Lancet 2010; 376(9753): 1670-81. https://www.ncbi.nlm.nih.gov/pubmed/21067804

Simvastatin 40 mg, oral (secondary prevention of ischaemic events): Naci H, Brugts JJ, Fleurence R, Ades A. Dose-comparative effects of different statins on serum lipid levels: a network meta-analysis of 256,827 individuals in 181 randomized controlled trials. European journal of preventive cardiology 2013; 20(4): 658-70. https://www.ncbi.nlm.nih.gov/pubmed/23529608

[xxvi]Atorvastatin 10 mg, oral (secondary prevention of ischaemic events – patients on protease inhibitors): Chastain DB, Stover KR, Riche DM. Evidence-based review of statin use in patients with HIV on antiretroviral therapy. J Clin Transl Endocrinol. 2017 Feb 22;8:6-14. https://www.ncbi.nlm.nih.gov/pubmed/29067253

Atorvastatin 10 mg, oral (secondary prevention of ischaemic events – patients on protease inhibitors): National Department of Health. Affordable Medicines, EDP-Primary Health Care. Cost-effectiveness analysis of high, intermediate, and low dose statins for the secondary prevention of cardiovascular disease, 31 January 2018. www.health.gov.za/

Atorvastatin 10 mg, oral (secondary prevention of ischaemic events – patients on protease inhibitors): Cholesterol Treatment Trialists' (CTT) Collaboration. Efficacy and safety of more intensive lowering of LDL cholesterol: a meta-analysis of data from 170 000 participants in 26 randomised trials. The Lancet 2010; 376(9753): 1670-81. https://www.ncbi.nlm.nih.gov/pubmed/21067804

Atorvastatin 10 mg, oral (secondary prevention of ischaemic events – patients on protease inhibitors): Naci H, Brugts JJ, Fleurence R, Ades A. Dose-comparative effects of different statins on serum lipid levels: a network meta-analysis of 256,827 individuals in 181 randomized controlled trials. European journal of preventive cardiology 2013; 20(4): 658-70. https://www.ncbi.nlm.nih.gov/pubmed/23529608

Atorvastatin, oral (drug-drug interaction with protease inhibitors): University of Liverpool. HIV drug interaction database. https://www.hiv-druginteractions.org/

[xxvii] Simvastatin 40 mg, oral (amlodipine drug interaction): Nishio S, Watanabe H, Kosuge K, Uchida S, Hayashi H, Ohashi K. Interaction between amlodipine and simvastatin in patients with hypercholesterolemia and hypertension. Hypertens Res. 2005;28(3):223–7. https://www.ncbi.nlm.nih.gov/pubmed/16097365

Simvastatin 40 mg, oral (amlodipine drug interaction): Son H, Lee D, Lim LA, Jang SB, Roh H, Park K. Development of a pharmacokinetic interaction model for co-administration of simvastatin and amlodipine. Drug Metab Pharmacokinet. 2014;29(2):120–8. https://www.ncbi.nlm.nih.gov/pubmed/23965645

[xxviii] High dose statins (management of adverse drug reactions): NICE: Cardiovascular disease: risk assessment and reduction, including lipid modification. Clinical guideline, 18 July 2014. www.nice.org.uk/guidance/cg181

[xxix]Aspirin: DeBerardis G, Sacco M, Strippoli GF, Pellegrini F, Graziano G, Tognoni G, Nicolucci A. Aspirin for primary prevention of cardiovascular events in people with diabetes: meta-analysis of randomised controlled trials. BMJ. 2009 Nov6;339:b4531.http://www.ncbi.nlm.nih.gov/pubmed/19897665

[xxx]Bisphosphonates, IV (therapeutic grouping): National Department of Health: Affordable Medicines, EDP-Adult Hospital level. Medicine Review: Bisphosphonates, therapeutic class for hypercalcaemia, including primary hyperparathyroidism, September 2017. http://www.health.gov.za/

Bisphosphonates, IV (therapeutic grouping): Ross JR, Saunders Y, Edmonds PM, Patel S, Wonderling D, Normand C, Broadley K. A systematic review of the role of bisphosphonates in metastatic disease. Health Technol Assess. 2004;8(4):1-176. https://www.ncbi.nlm.nih.gov/pubmed/14960258

Zoledronic acid, IV (dosing): The Society for Endocrinology, Metabolism and Diabetes of South Africa Type 2 Diabetes Guidelines Expert Committee. The 2017 SEMDSA Guideline for the Management of Type 2 Diabetes Guideline Committee. JEMDSA 2017; 21(1)(Supplement 1): S1-S196.
http://www.jemdsa.co.za/index.php/JEMDSA/article/view/647/937

Zoledronic acid, IV (dosing): South African Medicines Formulary. 12th Edition. Division of Clinical Pharmacology. University of Cape Town, 2016.

[xxxi] Corticosteroids, oral (intermediate-acting therapeutic class): South African Medicines Formulary. 12th Edition. Division of Clinical Pharmacology.University of Cape Town. 2016.

[xxxii] Calcium gluconate 10%, infusion (serum calcium <2 mmol/L): Tohme JF, Bilezikian JP. Diagnosis and treatment of hypocalcaemic emergencies. The Endocrinologist. 1996; 10-18.
http://journals.lww.com/theendocrinologist/Abstract/1996/01000/Diagnosis_and_Treatment_of_Hypocalcemic.3.aspx

[xxxiii]Hypothyroidism in pregnancy: Vadiveloo T, Mires GJ, Donnan PT, Leese GP. Thyroid testing in pregnant women with thyroid dysfunction in Tayside, Scotland: the thyroid epidemiology, audit and research study (TEARS). ClinEndocrinol (Oxf) 2013; 78:466.http://www.ncbi.nlm.nih.gov/pubmed/22548296

Hypothyroidism in pregnancy: Yassa L, Marqusee E, Fawcett R, Alexander EK. Thyroid hormone early adjustment in pregnancy (the THERAPY) trial. J ClinEndocrinolMetab 2010; 95:3234.
http://www.ncbi.nlm.nih.gov/pubmed/20463094

Hypothyroidism in pregnancy: Alexander EK, Marqusee E, Lawrence J, Jarolim P, Fischer GA, Larsen PR. Timing and magnitude of increases in levothyroxine requirements during pregnancy in women with hypothyroidism. N Engl J Med. 2004 Jul 15;351(3):241-9.http://www.ncbi.nlm.nih.gov/pubmed/15254282

Hypothyroidism in pregnancy: Abalovich M, Gutierrez S, Alcaraz G, Maccallini G, Garcia A, Levalle O. Overt and subclinical hypothyroidism complicating pregnancy. Thyroid. 2002 Jan;12(1):63-8.

http://www.ncbi.nlm.nih.gov/pubmed/11838732
[xxxiv]Limited alcohol intake (osteoporosis): Kanis JA, Johansson H, Johnell O, Oden A, De Laet C, Eisman JA, Pols H, Tenenhouse A. Alcohol intake as a risk factor for fracture. Osteoporos Int. 2005 Jul;16(7):737-42. https://www.ncbi.nlm.nih.gov/pubmed/15455194
[xxxv]Vitamin D, oral (dosing): South African Medicines Formulary. 12th Edition. Division of Clinical Pharmacology. University of Cape Town. 2016.
[xxxvi]Calcium: Bolland MJ, Leung W, Tai V, Bastin S, Gamble GD, Grey A, Reid IR. Calcium intake and risk of fracture: systematic review. BMJ. 2015 Sep 29;351:h4580. http://www.ncbi.nlm.nih.gov/pubmed/26420387
Vitamin D: Bolland MJ, Leung W, Tai V, Bastin S, Gamble GD, Grey A, Reid IR. Calcium intake and risk of fracture: systematic review. BMJ. 2015 Sep 29;351:h4580. http://www.ncbi.nlm.nih.gov/pubmed/26420387
[xxxvii]Bisphosphonates, oral (therapeutic class): Davis S, Martyn-St James M, Sanderson J, Stevens J, Goka E, Rawdin A, et al. A systematic review and economic evaluation of bisphosphonates for the prevention of fragility fractures. Health Technol Assess 2016;20(78). https://www.ncbi.nlm.nih.gov/pubmed/27801641
Bisphosphonates, oral (therapeutic class): National Department of Health: Affordable Medicines, EDP-Adult Hospital level. Medicine Review: Bisphosphonates, oral therapeutic class for secondary prevention of fragility fractures, 31 October 2017. http://www.health.gov.za/
Bisphosphonates, oral (secondary prevention of steroid-induced bone loss): Allen CS, Yeung JH, Vandermeer B, Homik J. Bisphosphonates for steroid-induced osteoporosis. Cochrane Database Syst Rev. 2016 Oct 5;10:CD001347. https://www.ncbi.nlm.nih.gov/pubmed/27706804
[xxxviii]Desmopressin, oral/IV/SC/nasal spray: Oiso Y, Robertson GL, Nørgaard JP, and Juul KV. Treatment of Neurohypophyseal Diabetes Insipidus. J Clin Endocrinol Metab 98: 3958–3967, 2013. https://www.ncbi.nlm.nih.gov/pubmed/23884783
Desmopressin, oral/IV/SC/nasal spray: British National Formulary, March 2017-September 2018. https://www.bnf.org/
[xxxix]Doxazosin: van der Zee PA, de Boer A. Pheochromocytoma: a review on preoperative treatment with phenoxybenzamine or doxazosin. Neth J Med. 2014 May;72(4):190-201. http://www.ncbi.nlm.nih.gov/pubmed/24829175
[xl]β-blockers (after adequate α-blockade): Lenders JW, Duh QY, Eisenhofer G, Gimenez-Roqueplo AP, Grebe SK, Murad MH, Naruse M, Pacak K, Young WF Jr, Endocrine Society. Pheochromocytoma and paraganglioma: an endocrine society clinical practice guideline. J Clin Endocrinol Metab. 2014 Jun;99(6):1915-42.https://www.ncbi.nlm.nih.gov/pubmed/24893135
[xli] Atenolol, oral: South African Medicines Formulary. 12th Edition. Division of Clinical Pharmacology. University of Cape Town. 2016.
[xlii] Corticosteroids, oral (intermediate-acting therapeutic class): South African Medicines Formulary. 12th Edition. Division of Clinical Pharmacology.University of Cape Town. 2016.
[xliii] Carbimazole: South African Medicines Formulary. 12th Edition. Division of Clinical Pharmacology. University of Cape Town. 2016.

CHAPTER 9
SYSTEMIC AND HEALTHCARE-ASSOCIATED INFECTIONS

ANTIMICROBIAL STEWARDSHIP

Antimicrobial stewardship refers to a systematic approach to optimising the appropriate use of an antibiotic to improve patient outcome(s) and limit emergence of resistant pathogens, whilst ensuring patient safety. It is one arm of the national and international response to the increasing public health crisis of antibiotic resistance. A critical component is adequate infection control. Antibiotics should only be used for the treatment and prevention of bacterial infections. The following checklist will help optimise prescribing:

Checklist for optimal antibiotic prescribing
1. **Medicine** – which is the narrowest-spectrum antibiotic that I can use to treat this bacterial infection?
2. **Dose** – many antibiotics require weight-based dosing, and their dosing depends on renal and/or hepatic function.
3. **Dose frequency** – dependent on the half-life of the drug and whether the activity of the antibiotic depends on the time above the MIC, the peak concentration relative to MIC, or the area under the concentration/time curve. Guidance for dosing frequency may require therapeutic drug monitoring, e.g. vancomycin and aminoglycosides.
4. **Duration** – should be dictated by evidence from randomised controlled trials whenever possible. Expert opinion from national and international guidelines should be consulted where evidence is weak.
5. **Route** – most antibiotics have good oral bioavailability, but some infections will require intravenous therapy either for the whole or part of the course. Patients who are critically ill, or who would be expected to have impaired gastrointestinal absorption of medicines (e.g. excessive vomiting) may also require intravenous antibiotics initially.
6. **De-escalation** – applies to the spectrum of antibiotic use and route of administration. All attempts to convert early from parenteral to oral use should be made.
MIC = minimum inhibitory concentration. Further guidance on local antimicrobial stewardship can be found online: https://www.health.gov.za/nhi-edp-amr/

9.1 HEALTHCARE-ASSOCIATED AND HOSPITAL ACQUIRED INFECTIONS

DEFINITION AND PRINCIPLES

Patients with healthcare associated and hospital acquired infections are at increased risk of being infected with drug resistant organisms. A hospital acquired infection is a new infection that develops after at least 48 hours of hospitalisation without evidence that the infection was present or incubating at the time of admission. Healthcare-associated infections should also be considered in persons with extensive healthcare contact such as: residence in a nursing home or other long-term care facility, hospitalisation in an acute care hospital for >2 days during the prior 90 days, or attendance at a hospital or haemodialysis clinic during the prior 30 days.

It is essential to obtain specimens for culture and sensitivity testing in all cases before starting antibiotics.

Empiric therapy suggestions below are only rough guidelines due to heterogeneity of resistance patterns between facilities and over time. Close liaison with regional microbiologists and regular review of hospital antibiotic policy based on local resistance patterns are essential.

9.1.1 INTRAVASCULAR CATHETER INFECTIONS

L53.9/T80.2 + (B95.8/Y84.8/B37.8)

PERIPHERAL LINE INFECTION:

Common organisms:

» coagulase negative staphylococci, particularly *S. epidermis,*
» *S. aureus.*

GENERAL MEASURES

» **NB: Always remove the intravascular line at the site of infection.**
» Small, localised areas of erythema at the catheter insertion site will usually resolve without antibiotic therapy after catheter removal.

MEDICINE TREATMENT

Patients with larger areas of erythema and tenderness extending beyond the insertion site who are systemically well:

LoE:IIIb[i]

- Clindamycin, oral, 450 mg 8 hourly for 5 days. A

If patients are systemically unwell, they should be treated as for a central venous catheter related systemic blood infection.

SHORT-TERM CENTRAL VENOUS CATHETER INFECTION: GENERAL MEASURES

Obtain microbiologic specimens: peripheral blood culture, blood culture from central catheter prior to removal, and culture of the catheter tip.

If peripheral blood culture is negative but central catheter culture is positive:

» Monitor closely for signs of infection and repeat peripheral blood cultures accordingly.

» If central line has grown *S. aureus*, 5-7 days of treatment is recommended (provided that peripheral blood cultures remain negative).

If peripheral blood culture is positive:

» Remove catheter, and treat with systemic antibiotics, guided by the culture results.

» Duration of antibiotic therapy should generally be for 48–72 hours after resolution of fever except for:

LoE:IIIb[ii]

– confirmed *S. aureus* infection, and

– candidaemia,

where treatment should be continued for 2 weeks after the 1st negative

LoE:IIIb[iii]

blood culture.

» For candidaemia and *S. aureus* infection, perform blood cultures every 2-3 days after therapy has been initiated until 2 consecutive cultures are negative, and 2 weeks after the 1st negative blood culture.

Empiric antibiotic therapy (prior to obtaining susceptibility results):

***S. aureus* infection** (B95.8/Y84.8)

- Vancomycin, IV, 25–30 mg/kg, empirically as a loading dose. W
  - Follow with 15–20 mg/kg/dose 12 hourly. (See Appendix II for guidance on prescribing and therapeutic drug monitoring.)

LoE:IIIa[iv]

  - Tailor therapy to drug-susceptibility results.

Candidaemia (B37.8/Y84.8)

» Candida isolated from blood culture should **always** be treated, even if the fever has settled after line removal because of a high risk of late complications.

» Candidaemia with species other than Candida albicans is becoming increasingly common – these species are often resistant to azoles.

» Treatment duration should extend for a minimum of two weeks following the first negative blood culture.

Empiric antifungal therapy:

LoE:IIa[v]

- Amphotericin B, IV, 0.7 mg/kg daily.

LoE:Ia[vi]

  - Ensure adequate hydration to minimise nephrotoxicity. (See Appendix II for preventing, monitoring and management of toxicity.)

Follow up susceptibility:
Once improved, if sensitive, complete course with:

LoE:IIa[vii]

- Fluconazole, oral, 400 mg daily.

If invasive candidiasis (resistant to fluconazole/amphotericin B or renal impairment is present and amphotericin B cannot be used):

- Echinocandins. (Specialist motivation.)

LoE:IIIb[viii]

REFERRAL/CONSULTATION

» *S. aureus* endocarditis.

9.1.2 SURGICAL WOUND INFECTIONS

T81.4 + (Y83.0-6/Y83.8-9/B95.6/U82.1)

DESCRIPTION

Gram positive bacteria, especially *S. aureus*, are the commonest cause.
Gram negative and anaerobic bacteria are important causes following gynaecological and intestinal surgery.

GENERAL MEASURES

» Microbiologic specimen (in patients with a larger area of erythema or systemic evidence of infection): deep wound swab (NOT a superficial swab), aspirate of pus, or tissue biopsy, and blood culture.
» Suture removal plus incision and drainage is essential.
» Antibiotics are not usually necessary unless there is marked surrounding cellulitis or features of systemic infection.

MEDICINE TREATMENT

Empiric antibiotic therapy:
Total duration of therapy should not exceed 7 days.

If surrounding cellulitis or systemic sepsis does not involve the gastro-intestinal (GI) or female genital tract:

LoE:IIa[ix]

- Cefazolin, IV, 1 g 8 hourly. A

Check Gram stain of exudate. If organism is gram negative:
STOP cefazolin and give:

LoE:IVb

- Piperacillin/tazobactam, IV, 4.5 g 8 hourly. W

Follow with oral therapy as soon as patient can swallow, and the temperature is <37.8°C for 24 hours:

LoE:IVb[x]

- Flucloxacillin, oral, 500 mg 6 hourly. A

Severe penicillin allergy: (Z88.0)

- Clindamycin, IV, 600 mg 8 hourly. A

Check Gram stain of exudate. If organism is gram negative:

ADD:

LoE:Ia[xi]

- Ertapenem, IV, 1 g daily. W

Follow with oral therapy as soon as patient can swallow and the temperature has been <37.8°C for 24 hours, based on culture results:

LoE:IIIb[xii]

- Clindamycin, oral, 450 mg 8 hourly. A

If surgery involved female uro-genital tract open GIT:

T81.4 + (Y83.6/Y83.8)

- Ceftriaxone, IV, 2 g daily. W

AND

LoE:IIIb[xiii]

- Metronidazole, IV, 500 mg 8 hourly. A

Methicillin (cloxacillin) resistant *S. aureus* (MRSA):

T81.4 + (B95.6+U82.1+Y83.9)

- Vancomycin, IV, 25–30 mg/kg as a loading dose. W
  - Follow with 15–20 mg/kg/dose 12 hourly. See Appendix II for guidance on prescribing and monitoring.

LoE:IIIb[xiv]

9.1.3 HOSPITAL-ACQUIRED PNEUMONIA (HAP) AND VENTILATOR-ASSOCIATED PNEUMONIA (VAP)

J12.0-3/J12.8-9/J13/J14/J15.0-9/J16.0/J16.8/J18.0-2/J18.8-9 + (Y95)

DESCRIPTION

HAP is defined as a new lung infiltrate (not present on admission) plus clinical evidence that the infiltrate is an infection (e.g. new onset of fever, purulent

sputum, leukocytosis) occurring >48 hours after admission to hospital. HAP has a high morbidity and mortality; early appropriate antibiotic therapy is essential.

Infection may be due to multi-drug resistant organisms, particularly in patients with prior intravenous antibiotic use within 90 days. LoE:IIa[xv]

Ventilator-associated pneumonia (VAP) occurs >48 hours after intubation. VAP is more often due to multi-drug resistant organisms than HAP.

GENERAL MEASURES

» Microbiologic specimens: blood culture and sputum/tracheal aspirate bacterial culture. Therapy should be adjusted according to culture result. A good quality Gram stain may be useful in guiding the choice of initial therapy.
» If patient is neutropenic – See Section 2.2: Febrile neutropenia.

MEDICINE TREATMENT

Empiric antibiotic therapy

LoE:IIa[xvi]

» Treatment duration: 7 days.
» Antibiotic choice should be based on local susceptibility patterns. (See National Institute for Communicable Diseases (NICD) AMR Dashboard: www.nicd.ac.za).

- Piperacillin/tazobactam, IV, 4.5 g 8 hourly. W

AND

LoE:IIIb[xvii]

- Amikacin, IV, 15 mg/kg daily. W (See Appendix II, for individual dosing and monitoring for response and toxicity.)

OR ALTERNATIVELY:

LoE:IIIb[xviii]

- Cefepime, IV, 2 g 12 hourly as monotherapy. W (See Appendix II for guidance on dosing in renal impairment.)

If high local resistance rates to the above regimens, then consider carbapenem with activity against Pseudomonas:

- Imipenem/cilastatin, IV, 1000/1000 mg 8 hourly as monotherapy. W

LoE:IIIb[xix]

OR

- Meropenem, IV, 2 g 8 hourly as monotherapy. W

LoE:IVb[xx]

Note:
» De-escalate as soon as the culture is available.
» For severe pencillin allergy, consult an infectious diseases specialist or microbiologist.

9.1.4 URINARY TRACT INFECTIONS, CATHETER ASSOCIATED

T83.5 + (Y84.6+N39.0)

DESCRIPTION

» Common organisms: resistant aerobic gram-negative bacteria.
» Microbiologic specimen: blood culture and Mid-stream/Catheter specimens of urine (MSU/CSU) for microscopy and bacterial culture.
» In most patients with long-term catheters, bacteria cultured on CSU represent colonisation rather than infection – only treat with antibiotics if features of sepsis or pyelonephritis are present.

GENERAL MEASURES

» Remove catheter.

MEDICINE TREATMENT

Empiric antibiotic therapy:

- Amikacin, IV, 15 mg/kg daily for 7 days. A

OR

If local resistance patterns show low level resistance to ciprofloxacin or culture shows sensitivity:

LoE:IIIb[xxi]

- Ciprofloxacin, oral, 500 mg 12 hourly for 7 days. W

9.2 ADULT VACCINATION

Note: As COVID vaccination recommendations are being updated regularly as new evidence emerges, please consult the latest National Department of Health vaccine policy recommendations.

Vaccine	Indications	Comments

• Influenza vaccine Z25.1	» Pregnant women » Elderly patients >65 years. » HIV-infected patients. » Patients with chronic pulmonary or cardiac conditions or malignancy » Healthcare workers with direct patient contact. *	○ Contraindication: <6 months of age. ○ Dose: IM, 0.5 mL ○ Repeat annually. ○ Severe egg allergy is not an absolute contraindication to the inactivated influenza vaccine. However, it is recommended that individuals reporting a history of severe egg allergy are vaccinated in a setting equipped to manage allergic reactions.
• Pneumococcal vaccine (23 valent polysaccharide) Z23.8	» Asplenic patients. » Chronic cerebrospinal fluid (CSF) leak.	○ Contraindication: pregnancy. ○ Dose: IM, 0.5 mL Booster: after 5 years and at 65 years of age. *LoE:IIIb*[xxii]
• Hepatitis B vaccine** Z24.6	» High risk groups, e.g. hospital personnel or sexual contacts of infected patients. » Sexual assault.	○ Dose: IM, 1 mL immediately then 1 mL after 1 month and 1 mL 6 months after 1st dose. ○ Administer deep IM in deltoid muscle.
• Tetanus toxoid vaccine Z23.5	» Booster when there is a high risk for tetanus (unless given in previous 5 years) e.g. contaminated wound or pregnant women to prevent neonatal tetanus.	○ Dose: IM, 40 IU (0.5 mL).

Table 9.1: Adult vaccination

*Healthcare workers are not routinely offered immunisation during the annual campaign. Although it is recommended that healthcare workers are vaccinated against influenza, they will not be provided with publicly funded vaccines unless they fall within any of the designated high-risk groups.

** Not to be given to patients who have already been immunised.

Note: Prioritisation strategies may vary in a pandemic.

9.2.1 RABIES VACCINATION

Z24.2

*Rabies is a notifiable medical condition.

See the Primary Health Care STGs and EML - Section 21.3.1.1: Animal bites.

9.3 BRUCELLOSIS

A23.0-3/A23.8-9

*Notifiable medical condition.

DESCRIPTION

Zoonotic infection, usually due to *B. abortus* in South Africa. Infection is usually acquired from unpasteurised milk products or handling raw meat.

MEDICINE TREATMENT

- Doxycycline, oral, 100 mg 12 hourly for 6 weeks. A

AND

LoE:IVb[xxiii]

- Gentamicin, IV, 6 mg/kg daily for 3 weeks. A (See Appendix II for guidance on prescribing).
  - Preferred regimen for osteo-articular or cardiac involvement.

Alternatively, REPLACE gentamicin with rifampicin:

- Rifampicin, oral, 7.5 mg/kg 12 hourly for 6 weeks. W

Exclude TB before starting rifampicin-based therapy.

9.4 EMERGING RESPIRATORY PATHOGENS

9.4.1 MIDDLE EAST RESPIRATORY SYNDROME CORONAVIRUS INFECTION: MERS COV

B34.2/J16.8 + (B97.2)

*Notifiable medical condition.

Note: Consult most recent guidelines from the National Department of Health/ NICD.

DESCRIPTION

Middle East Respiratory Syndrome (MERS) is a viral respiratory illness caused by Middle East Respiratory Syndrome Coronavirus (MERS-CoV). Individuals with MERS-CoV present with a wide spectrum of clinical presentation, ranging from asymptomatic infection to acute upper respiratory illness and rapidly progressing lower respiratory illness, respiratory failure, septic shock, and multi-organ failure resulting in death.

A typical presentation of MERS includes:

- » Fever (>38°C)
- » Cough
- » Chills or rigors
- » Shortness of breath

Presentation may also include haemoptysis, sore throat, myalgias, diarrhoea, vomiting, and abdominal pain.

Complications:

- » Severe pneumonia
- » ARDS
- » Acute renal failure
- » Refractory hypoxaemia

GENERAL MEASURES

- » **Ensure that patients suspected to have MERS Coronavirus are isolated at all times to limit further exposure.**
- » Discuss and manage all suspected, probable cases and contacts in consultation with the regional virologist or infectious diseases specialist at the referral centre/NICD.
- » Transfer of patients should only occur once all relevant arrangements have been made to limit further exposure to a potential contagious and life threatening agent.
- » Record and follow-up all patient contacts.

Prevention

- » Practise handwashing and careful disposal of materials that are infected with nasal secretions.
- » Use antiseptic/disinfectant solutions containing choroxylenol, benzalkonium chloride, and/or cetrimide. Chlorhexidine has been shown to be ineffective.
- » Add droplet precautions to the standard precautions. Airborne precautions should be applied when performing aerosol-generating procedures.

MEDICINE TREATMENT

- » Treatment is supportive.
- » No antiviral agents or vaccines are currently available.

REFERRAL

- » All cases after consultation with infectious diseases specialist and NICD.

9.4.2 CORONAVIRUS DISEASE-19 (COVID-19)

U07.1/U07.2

*Notifiable medical condition.

Note: Consult the most recent NICD guidelines on the clinical management of suspected or confirmed Covid-19 disease, available at: https://www.nicd.ac.za/diseases-a-z-index/disease-index-covid-19/covid-19-guidelines/clinical-management-of-suspected-or-confirmed-covid-19-disease/

DESCRIPTION

Coronavirus Disease of 2019 (COVID-19) is a viral, respiratory illness caused by SARS-CoV-2. Infection may be asymptomatic, and the majority of symptomatic infections (>80%) are characteristed by mild upper- and/or lower

respiratory tract symptoms. However, a minority of patients may develop severe disease requiring supplementary oxygen or, in severe cases, mechanical ventilation.

A typical presentation of COVID-19 includes some or all of the following:
» fever, chills or rigors, cough, dyspnoea, anosmia, dysgeusia, myalgias, sore throat, nausea, vomiting and/or diarrhoea.
» Atypical presentations are increasingly being recongised, including large vessel strokes (see Section 14.1.1: Stroke) and diabetic ketoacidosis (see Section 8.6.2: Diabetic ketoacidosis [DKA] and hyperosmolar hyperglycaemic state [HHS]).

Complications:
» Refractory hypoxaemia
» Long-COVID
» ARDS
» MIS-C and MIS-A

Diagnosis
Samples should be sent for SARS-CoV-2 PCR testing. Upper respiratory tract samples from all suspected patients should be sent – a nasopharyngeal swab is preferred, but in patients where this is not possible (e.g. recent nasal surgery, or severe coagulopathy), an oropharyngeal, nasal mid-turbinate, or anterior nares swab can be collected instead. Lower respiratory tract samples (e.g. sputum, tracheal aspirates) may be sent in addition if available.

GENERAL MEASURES
» If COVID-19 is suspected, isolate patient to limit further exposure.
» Adhere to standard contact and droplet precautions.
» Apply precautions against airborne transmission when performing aerosol-generating procedures such as intubation or nasogastric suctioning.

Management
» Give supplemental oxygen if required, targeting an SpO_2 of ≥90% for non-pregnant adults (≥94% for pregant women). Titrate oxygen therapy to reach targets by means of a nasal cannula, simple face mask or face mask with a reservoir bag, as appropriate.

	Nasal cannula	Simple face mask	Face mask with reservoir bag
Flow rate	1-5 L/min	6-10 L/min	10-15 L/min
FiO_2 estimate	0.25-0.4	0.4-0.6	0.6-0.95

» Patients who have respiratory failure despite maximal face mask oxygen should be promptly identified and considered for possible escalation of

respiratory support with high flow nasal cannula oxygen, continuous positive airway presure, or intubation and mechanical ventilation as appropriate.

LoE:IIIb[xxiv]

» The use of the prone position in non-intubated, conscious patients who are hypoxaemic may be beneficial.

MEDICINE TREATMENT

Note: Antibiotics are of no value for the treatment of confirmed COVID-19 unless there is clear evidence of a co-existing infection.

Thromboprophylaxis: (Z29.2)
All hospitalised patients with COVID-19 require prophylaxis against venous thromboembolic disease, in the absence of any contraindications (see Section 2.8: Venous thrombo-embolism).

LoE:IIIb[xxv]

- Low molecular weight heparin, e.g.:
- Enoxaparin, SC, 40 mg daily.
  - Reduce dose to 20 mg daily in patients with renal failure (eGFR <30 mL/minute).

OR

- Unfractionated heparin, SC, 5 000 units 12 hourly.

Note: Patients with D-dimer >1.5 mg/L or requiring a non-rebreather mask or more should be considered for therapeutic doses of LMWH or unfractionated heparin (see Section 2.8: Venous thrombo-embolism).

LoE:IIIb[xxvi]

- Low molecular weight heparin, e.g.:
- Enoxaparin, SC, 1.5 mg/kg daily,

OR

- Enoxaparin, SC, 1 mg/kg 12 hourly.

In morbid obesity, dosing of LMWH should be individualised in discussion with a specialist.

In renal failure (eGFR <30 mL/minute), the recommended therapeutic dose of LMWH is 1 mg/kg daily.

Evidence indicates that PTT monitoring is not necessary with weight-based dosing of unfractionated heparin. However, in patients with morbid obesity and renal failure (eGFR <30 mL/minute), unfractionated heparin should be used with PTT monitoring to maintain the PTT at 1.5 to 2.5 times the control. PTT should be taken 4 hours after SC dose.

In non-pregnant patients who require supplemental oxygen:

LoE:Ia[xxvii]

- Corticosteroids, e.g.:
- Dexamethasone, IV, 6 mg daily for up to 10 days, or until discharge.

In pregnant patients who require supplemental oxygen:

If corticosteroids are also needed to accelerate fetal lung maturity:

See Section 6.11.1: Preterm labour (PTL) and preterm prelabour rupture of membranes (PPROM).

If corticosteroids are not needed for fetal lung maturity:

- Corticosteroids, e.g.:
- Dexamethasone, IV, 6 mg daily for up to 10 days, or until discharge.

If there is a concern of in-utero steroid exposure, use corticosteroid therapy with less placental transfer:

- Prednisone, oral 40 mg daily, for up to 10 days, or until discharge.

OR

- Hydrocortisone, IV, 80 mg 12 hourly for up to 10 days, or until discharge.

Note:

LoE:IIIb[xxviii]

» See Section 6.5: COVID-19 in pregnancy.

Corticosteroids cross the placenta and may have long-term, deleterious effects on the child.

9.5 HAEMORRHAGIC FEVER SYNDROME

A98.0-5/A98.8/A99

*Notifiable medical condition.

DESCRIPTION

Characterised by high fever, together with disseminated intravascular coagulation (DIC) and bleeding tendency. Other symptoms and organ involvement vary according to the causative virus.

Some important causes other than viral haemorrhagic fevers (VHF) are:

» severe bacterial infections, particularly *N. meningitidis*,
» severe tick bite fever,
» severe falciparum malaria,
» fulminant hepatitis,
» leptospirosis, and
» other causes of DIC or bleeding tendency.

Endemic causes of VHF in South Africa are Crimean-Congo fever and Rift Valley fever, both of which may be transmitted between humans by means of blood and body fluids.

GENERAL MEASURES

» A detailed travel and clinical history are crucial.
» If VHF is suspected, isolate patient in a single room and take proper precautions to limit further exposure.
» Precautions should include:
  – long sleeved disposable gown,
  – vinyl or rubber apron if the patient is bleeding,
  – two pairs of latex gloves, one below the gown and one over the gown,
  – disposable face mask, preferably with a visor,
  – goggles if a mask is used without a visor, and
  – waterproof boots or 2 pairs of overshoes, one over the other.
» Exclude alternate diseases by means of appropriate laboratory testing.
» Testing for VHF may be required, both to confirm or, to exclude the possibility of VHF - this must be arranged with the NICD (see above), before sending the specimens, as specific precautions apply.
» Support patients with packed red cells and fresh frozen plasma, as required - see Section 23.5.2: Anaemia in critical care.
» Record and follow up all patient contacts.

Severe bacterial infections can mimic the features of haemorrhagic fever syndrome. Broad-spectrum antibiotics, e.g. ceftriaxone, IV, 2 g daily (W), are indicated in every case until the diagnosis is confirmed.

REFERRAL

» Discuss and manage all suspected VHF cases in consultation with the Regional Virologist or Infectious Diseases Consultant at the referral centre.
» Cases may also be discussed with the Special Pathogens Unit of the NICD:
  Tel: 011 386 6000, Outbreak hotline: 082 883 9920.
» Transfer of patients should only occur once all relevant arrangements have been made to limit further exposure to a potentially contagious and life-threatening virus.

9.6 HYDATID DISEASE

B67.0-9

DESCRIPTION

Cysts of *E. granulosus*, acquired from ingestion of helminth ova passed out in dog faeces, particularly in sheep-farming areas. Cysts may occur in any organ but are most commonly found in the liver and lungs.

GENERAL MEASURES

Definitive treatment with surgery or PAIR (**P**ercutaneous **A**spiration **I**njection of helminthicidal agent and **R**e-aspiration) is preferred for all accessible lesions.

MEDICINE TREATMENT

With medical therapy, cure is achieved in about half, improvement in about a quarter and no response, in about a quarter of cases:

- Albendazole, oral, 15 mg/kg/day up to maximum of 400 mg 12 hourly *LoE:IIIb[xxix]*
  with meals.
  - Duration is 3–6 months according to response on imaging for inoperable cysts **or** 14–28 days before and 28 days after *LoE:Ia[xxx]*
    PAIR/surgery.
  - Monitor liver function tests and FBCs monthly.

REFERRAL

All cases to a centre with experience in surgery and PAIR.

9.7 MALARIA

See the Primary Health Care STGs and EML - Section 10.7: Malaria.

9.7.1 MALARIA, UNCOMPLICATED

B50.0/B50.8-9/B51.0/B51.8-9/B52.9/B53.0/B53.8/B54

*Notifiable medical condition.

See the Primary Health Care STGs and EML - Section 10.7.1: Malaria, non-severe/uncomplicated.

9.7.2 MALARIA, SEVERE

B50.0/B50.8

*Notifiable medical condition.

See the Primary Health Care STGs and EML - Section 10.7.2: Malaria, severe/complicated.

DESCRIPTION

P. falciparum malaria with one or more of the following features:

- severe general body weakness (prostration)
- impaired consciousness
- renal dysfunction
- abnormal bleeding (e.g. epistaxis)
- convulsions
- heavy parasitaemia (≥5%)

» repeated vomiting
» severe diarrhoea
» severe anaemia (Hb <6 g/dL)
» haemoglobinuria
» acidosis (plasma bicarb <15 mmol/L)
» ARDS
» shock
» hypoglycaemia
» clinical jaundice

GENERAL MEASURES

» Maintain hydration but avoid excessive fluid administration as this could contribute to the development of ARDS (especially in pregnancy).
» Transfuse if haemoglobin <6 g/dL.
» There is no convincing evidence of benefit for the use of exchange transfusion.

MEDICINE TREATMENT

Intravenous therapy:

- Artesunate, IV, 2.4 mg/kg at 0, 12 and 24 hours; then daily until patient is able to tolerate oral therapy.
  - Administer at least 3 IV doses before switching to oral artemether/lumefantrine.

LoE:Ia[xxxi]

Follow intravenous therapy with oral therapy:

- Artemether/lumefantrine 20/120 mg, oral, 4 tablets per dose, taken with fat-containing food or full cream milk to ensure adequate absorption.
  - Give the first dose immediately.
  - Give the second dose 8 hours later.
  - Then 12 hourly for another 2 days. (6 doses given over 3 days, i.e. 24 tablets in total).

» Monitor treatment response with regular blood smears.
» An increase in parasitaemia may occur within 24 hours due to release of sequestrated parasites, but a reduction should be seen after 48 hours.
» Gametocytes may appear after this stage – this does NOT mean failure of therapy as gametocytes may persist for up to 2 weeks after successful therapy. Only the reappearance of trophozoites or failure to clear them means failure.

Consider concomitant bacteraemia in patients with severe malaria, especially if they have neutrophilia.

REFERRAL

» Patient in need of ventilation or dialysis if these are unavailable on site.

9.8 SCHISTOMIASIS

B65.0-3/B65.8-9

*Notifiable medical condition.

DESCRIPTION

A parasitic infestation with:

» *Schistosoma haematobium*: primarily involves the bladder and renal tract, or
» *Schistosoma mansoni*: primarily involves the intestinal tract.

Acute schistosomiasis syndrome

» Typically occurs in travellers to endemic areas with freshwater exposure 3-7 weeks before onset.
» Clinical features include fever, rigors/chills, urticaria, angioedema, myalgias, arthralgias, dry cough, diarrhoea, abdominal pain, and headache. Symptoms are usually relatively mild and resolve spontaneously over a period of a few days to a few weeks.
» The eosinophil count is almost invariably markedly elevated.
» Diagnosis is confirmed serologically – eggs are seldom seen in stool or urine.
» Differential diagnosis includes urinary tract infection; glomerulonephritis; HIV; gastroenteritis (Salmonella); hepatitis A, B and C; and malaria.

Chronic schistosomiasis

» Most individuals with schistosomiasis infection are asymptomatic.
» *S. haematobium* may present with macroscopic haematuria and urinary symptoms. Chronic bladder involvement and urinary tract involvement may cause urinary incontinence and obstructive uropathy.
» *S. mansoni* may present with chronic or intermittent dysentery. Periportal fibrosis and portal hypertension may occur.
» Pulmonary hypertension and central nervous system involvement (particularly myelopathy) are uncommon complications.
» Definitive diagnosis is by finding eggs in urine (*S. haematobium*), stool (*S. mansoni*), or on biopsy. Serology is usually positive.

MEDICINE TREATMENT

Acute schistosomiasis syndrome

- Corticosteroids (intermediate-acting) e.g.:
- Prednisone, oral, 40 mg daily for 5 days.

LoE:IIIb[xxxii]

Note: Praziquantel may cause life-threatening deterioration if given in acute schistosomiasis.

<u>4-6 weeks later, after symptoms have resolved:</u>

- Praziquantel, oral, 40 mg/kg as a single dose.

LoE:IIIb[xxxiii]

AND

- Corticosteroids (intermediate-acting) e.g.:
- Prednisone, oral, 40 mg daily for 5 days.

Note: Optimum time for administration of praziquantel is uncertain but sufficient time is required for the worms to mature.

If eosinophilia and high antibody titres are still present after 4-6 weeks, repeat praziquantel treatment:

LoE:IIIb[xxxiv]

- Praziquantel, oral, 40 mg/kg as a single dose.

Chronic schistosomiasis

Manage as recommended in PHC STGs and EML, Section 10.12: Schistosomiasis (bilharzia).

9.9 TETANUS

A35

*Notifiable medical condition.

DESCRIPTION

Painful muscle spasms and rigidity following inoculation by trauma of *Clostridium tetani* spores, which germinate and produce toxins. The wound may be trivial, and healing may have occurred before presentation. Incubation period is 3-21 days. Tetanus may be localised, with muscle spasms near the site of inoculation, or generalised, with spasm of the jaw muscles being a common presenting sign.

GENERAL MEASURES

» These patients need to be managed in a high care setting where ventilation is available.
» Maintain and protect airway.
» Monitor ECG and blood pressure.
» Maintain and replace IV fluids.
» Wound management is essential with debridement and removal of any foreign bodies.

MEDICINE TREATMENT

For rigidity, spasms: (R25.2)

- Diazepam, IV, 10 mg 4 hourly for 24 hours.
  - Consider switch to oral therapy after 24 hours as prolonged parenteral diazepam administration can cause acidosis.

LoE:IIIb[xxxv]

  - Titrate to effect: doses as high as 50–100 mg two hourly may be required.
  - Higher doses require monitoring for respiratory depression.
  - Use muscle relaxants sparingly as these may exacerbate autonomic instability.

Antibiotic treatment:

LoE:IIIb[xxxvi]

- Metronidazole, IV, 500 mg 8 hourly for 10 days. A

For passive immunisation: (Z23.5)

- Tetanus immunoglobulin, IM, 3 000 units as a single dose.

For active immunisation of all patients (as clinical tetanus does not always confer immunity): (Z23.5)

- Tetanus toxoid vaccine, IM, 0.5 mL, total of 3 doses:
  - on admission,
  - at 4 weeks, and
  - at 6 months.
  - Administer at a different site to that used for administering tetanus immunoglobulin.

For pain:

- Paracetamol, oral, 500 mg to1 g, 4 to 6 hourly as required (to a maximum of 4 g in 24 hours).
  - Maximum dose: 15 mg/kg/dose.

LoE:IIa[xxxvii]

- Morphine, IV, to a total maximum dose of 10 mg. (See Appendix II, for individual dosing and monitoring for response and toxicity.)

For shock, dehydration, maintenance of hydration: R57.9 + (A35)

- IV fluids.

For prophylaxis for deep vein thrombosis: (Z29.2)

See Section 2.8.1: Venous thrombo-embolism - Prophylaxis.

REFERRAL

» All cases to a facility with resources for artificial mechanical ventilation.

9.10 TICK BITE FEVER

A77.0-3/A77.8-9/A93.8

DESCRIPTION

Tick-borne infection due to *R. conorii*, acquired from dogs, or *R. africae*, acquired from cattle and game. The hallmark of tick bite fever is the eschar, a round black lesion ± 5 mm in diameter with an inflammatory halo that occurs in about two thirds of patients with *R. conorii* and in most cases of *R. africae* infection, where multiple eschars are common. A rash develops on about the third day of illness in about two thirds of patients with *R. conorii* (less common

with *R. africae* infection). In *R. conorii* infection the rash is maculopapular and involves the palms and soles. In *R. africae* infection the rash is sparse and may be vesicular. Headache is a prominent symptom.

MEDICINE TREATMENT

Non-pregnant:

Treatment duration: Treat for 7 days (if afebrile), or until at least 3 days after the fever has subsided.

LoE:IIIb[xxxviii]

- Doxycycline, oral, 100 mg 12 hourly. A

LoE:IVb[xxxix]

If pregnant: O98.5 + (A77.0-3/A77.8-9/A93.8)

LoE:IIIb[xl]

- Doxycycline, oral, 100 mg 12 hourly for 2 days. A

Then switch to:

- Azithromycin, oral, 500 mg once daily for 3 days. W

LoE:IIIb[xli]

<u>If patient is unable to tolerate oral therapy:</u>

- Ciprofloxacin, IV, 400 mg 8 hourly. W

Note: Ciprofloxacin has inferior efficacy compared to doxycycline. Oral doxycycline should be commenced as soon as possible.

<u>Note:</u>

LoE:Ivb[xlii]

» Tick bite fever responds rapidly to treatment. Fever persisting for >48 hours after initiation of treatment should prompt consideration of an alternative or additional diagnosis.

9.11 TYPHOID FEVER (ENTERIC FEVER)

A01.0-4

*Notifiable medical condition (Typhoid fever).

DESCRIPTION

Systemic infection due to *S. enteritica* serotype Typhi or related organisms (e.g. *S. paratyphi*, *S. choleraesuis*). Initial symptoms are abdominal pain, headache, cough and fever, with diarrhoea developing after a few days. Bacteraemia is common in the first week of illness, subsequently stool culture has the highest yield.

GENERAL MEASURES

» Transfusion is indicated for severe haemorrhage.
» Replace fluid and electrolytes.
» Contact isolation during acute phase of illness.

MEDICINE TREATMENT

Antibiotic therapy:

Note: There is increasing resistance to ciprofloxacin in South Africa. Ensure that specimens are sent for culture and sensitivity prior to commencing antibiotic therapy.

Total duration of antibiotic therapy: 10 days.

LoE:IIIb[xliii]

- Ceftriaxone, IV, 2 g 12 hourly. (W)

Follow with oral therapy as soon as patient can swallow and the temperature is <37.8°C for 24 hours, based on culture sensitivity results:

LoE:Ivb

- Ciprofloxacin, oral, 500 mg 12 hourly. (W)

Note:

» Stool cultures must be repeated at weekly intervals after clinical recovery to ensure that a carrier state has not developed.

» Two consecutive negative stool cultures are required to exclude carrier state. This is of vital importance in patients whose occupation includes handling of food, whereby negative stool culture results are required before they can be medically permitted to resume their occupational duties.

Chronic carriers: (Z22.0)

- Ciprofloxacin, oral, 500 mg 12 hourly for 6 weeks (W) (if sensitive to ciprofloxacin).
  - Advise strict hand washing.
  - Avoid food preparation for others during severe illness.

REFERRAL

» Surgical consultation for complications such as intestinal haemorrhage, threatening bowel perforation or localisation with metastatic infection with or without abscess formation, and peritonitis.

» Drug resistant organism: consult microbiology/infectious diseases services.

9.12 VARICELLA (CHICKENPOX), COMPLICATED

B01.1-2† + (G02.0*/G05.1*+J17.1*)/B01.8

GENERAL MEASURES

» Cool, wet compresses or tepid water baths.

» Body hygiene to prevent secondary infection.

» Advise against scratching.

MEDICINE TREATMENT

Antiviral therapy is required in complicated cases, e.g.:

» chickenpox pneumonia,

» pregnancy,

» neurological involvement, and

» chickenpox in immunocompromised patients.

Antiviral therapy:
Aciclovir, IV, 10 mg/kg 8 hourly for 7 days.
- Infuse aciclovir over one hour.

For varicella without neurological involvement, when the patient's clinical condition improves, the 7-day course can be completed with:

LoE:IVb[xliv]

- Antiviral (active against varicella zoster), e.g:
- Aciclovir, oral, 800 mg five times daily.
  - Doses are given 4 hourly, except for dose scheduled for the middle of the night.

Secondary infection
B02.8
Treat secondary bacterial infection if suspected.

- Flucloxacillin, oral, 500 mg 6 hourly for 5 days. A
  OR
- Cefalexin, oral, 500 mg 6 hourly for 5 days. A

Passive immunization following significant exposure: (Z29.1)
Criteria for eligibility [both a) and b) below are required]:
a) Significant exposure - household contacts exposed to/ patients lying adjacent to (same ward) those diagnosed with varicella.
b) Severe immunological compromise and lack of varicella-directed immunity (i.e. no history of chickenpox/shingles, or negative VZV IgG).

- Varicella-zoster immunoglobulin (VZIG), IM, 125 units/10 kg.
  - Maximum dose: 600 units.

LoE:IVb[xliv]

  - Administer within 96 hours of significant exposure.

9.13 ZOSTER (SHINGLES)
B02.9

DESCRIPTION
Dermatomal eruption of vesicles on an erythematous base due to varicella-zoster virus (lies dormant in nerve ganglia following chickenpox).

GENERAL MEASURES
» Isolate from immunocompromised or pregnant non-immune individuals (who may develop severe chickenpox).
» Offer HIV test, especially in patients <50 years of age.

MEDICINE TREATMENT

Antiviral therapy should be provided for:

» Immunocompromised patients, provided that active lesions are still being formed, and
» Immunocompetent individuals provided they present within 72 hours of onset of clinical symptoms.

- Antiviral (active against herpes zoster) e.g.:
- Aciclovir, oral, 800 mg five times daily for 7 days *LoE:IVb*[xlvi]

(given 4 hourly except for the dose scheduled for the middle of the night).

For zoster with secondary dissemination or neurological/ complicated eye involvement (i.e. complicated herpes zoster ophthalmicus e.g. acute retinal necrosis (ARN), optic neuropathy or orbitopathy):

B02.0-3†+(H03.1*/H13.1*/H19.2*/H19.0*/H22.0*)/ B02.7+(G02.0*/G05.1*/G53.0*/ G63.0*)/B02.8

- Aciclovir, IV, 10 mg/kg 8 hourly for 7 days.
  - Infuse aciclovir over one hour.
  - The course can be completed with aciclovir, oral, 800 mg five times daily.
  - Dose adjustment based on renal clearance. (See Appendix II for guidance on prescribing and monitoring.) *LoE:IVb*[xlvii]

Secondary infection

B02.8

This is seldom present and is over-diagnosed. The vesicles in shingles often contain purulent material, and erythema is a cardinal feature of shingles.
If there is suspected associated bacterial cellulitis:

- Flucloxacillin, oral, 500 mg 6 hourly for 5 days. A

For pain:

Pain is often very severe and requires active control. Combination of different classes of analgesics is often necessary.
Recommended therapy for acute phase of infection, e.g.:

- Paracetamol, oral, 500 mg to1 g, 4 to 6 hourly as required (to a maximum of 4 g in 24 hours).
  - Maximum dose: 15 mg/kg/dose.

AND/OR

If pain is not adequately controlled:

- Tramadol, oral, 50–100 mg 6 hourly.

See Chapter 26: Pain.

Post-herpetic neuralgia: B02.2+(G53.0*)
Initiate adjuvant therapy early if indicated.

- Amitriptyline, oral, 10 mg at night.

- Titrate as necessary to a maximum dose of 150 mg.

See Section 26.1.4: Neuropathic pain.

REFERRAL

» Refer to an ophthalmologist if there is ocular involvement with ophthalmic zoster (if the tip of the nose is involved then ocular involvement is much more likely). See Section 18.4: Herpes zoster ophthalmicus.
» Patients who develop complications e.g. myelitis.

References:

[i] Clindamycin, oral: South African Antibiotic Stewardship Programme. A Pocket Guide to Antibiotic Prescribing for Adults in South Africa, 2015.http://www.fidssa.co.za/images/SAASP_Antibiotic_Gudidelines_2015.pdf

Clindamycin, oral: South African Medicines Formulary. 14th Edition. Division of Clinical Pharmacology. University of Cape Town. 2022.

Clindamycin, oral: Bouazza N, Pestre V, Jullien V, Curis E, Urien S, Salmon D, Tréluyer JM. Population pharmacokinetics of clindamycin orally and intravenously administered in patients with osteomyelitis. Br J ClinPharmacol. 2012 Dec;74(6):971-7.http://www.ncbi.nlm.nih.gov/pubmed/22486719

[ii] Empiric parenteral antibiotic therapy (*S. aureus* infection): Chong YP, Moon SM, Bang KM, Park HJ, Park SY, Kim MN, Park KH, Kim SH, Lee SO, Choi SH, Jeong JY, Woo JH, Kim YS. Treatment duration for uncomplicated Staphylococcus aureus bacteremia to prevent relapse: analysis of a prospective observational cohort study. Antimicrob Agents Chemother. 2013 Mar;57(3):1150-6.http://www.ncbi.nlm.nih.gov/pubmed/23254436

Empiric parenteral antibiotic therapy (*S. aureus* infection): Liu C, Bayer A, Cosgrove SE, Daum RS, Fridkin SK, Gorwitz RJ, Kaplan SL, Karchmer AW, Levine DP, Murray BE, J Rybak M, Talan DA, Chambers HF; Infectious Diseases Society of America. Clinical practice guidelines by the infectious diseases society of america for the treatment of methicillin-resistant Staphylococcus aureus infections in adults and children. Clin Infect Dis. 2011 Feb 1;52(3):e18-55. http://www.ncbi.nlm.nih.gov/pubmed/21208910

[iii] Empiric candidaemia therapy (duration of 2 weeks): Pappas PG, Kauffman CA, Andes DR, Clancy CJ, Marr KA, Ostrosky-Zeichner L, Reboli AC, Schuster MG, Vazquez JA, Walsh TJ, Zaoutis TE, Sobel JD. Clinical Practice Guideline for the Management of Candidiasis: 2016 Update by the Infectious Diseases Society of America. Clin Infect Dis. 2016 Feb 15;62(4):e1-50. https://www.ncbi.nlm.nih.gov/pubmed/26679628

Empiric candidaemia therapy (duration of 2 weeks): Mermel LA, Allon M, Bouza E, Craven DE, Flynn P, O'Grady NP, Raad II, Rijnders BJ, Sherertz RJ, Warren DK. Clinical practice guidelines for the diagnosis and management of intravascular catheter-related infection: 2009 Update by the Infectious Diseases Society of America. Clin Infect Dis. 2009 Jul 1;49(1):1-45. . Erratum in: Clin Infect Dis. 2010 Apr 1;50(7):1079. Dosage error in article text. Clin Infect Dis. 2010 Feb 1;50(3):457. https://www.ncbi.nlm.nih.gov/pubmed/19489710

[iv] Vancomycin, IV: Reardon J, Lau TT, Ensom MH. Vancomycin loading doses: a systematic review. Ann Pharmacother. 2015 May;49(5):557-65. http://www.ncbi.nlm.nih.gov/pubmed/25712445

Vancomycin, IV: Rybak M, Lomaestro B, Rotschafer JC, Moellering R Jr, Craig W, Billeter M, Dalovisio JR, Levine DP. Therapeutic monitoring of vancomycin in adult patients: a consensus review of the American Society of Health-System Pharmacists, the Infectious Diseases Society of America, and the Society of Infectious Diseases Pharmacists. Am J Health Syst Pharm. 2009 Jan 1;66(1):82-98. Erratum in: Am J Health Syst Pharm. 2009 May 15;66(10):887. http://www.ncbi.nlm.nih.gov/pubmed/19106348

Vancomycin, IV: South African Medicines Formulary. 14th Edition. Division of Clinical Pharmacology. University of Cape Town. 2022.

[v] Antibiotic therapy (candidaemia): Takesue Y, Ueda T, Mikamo H, Oda S, Takakura S, Kitagawa Y, Kohno S; ACTIONs Project. Management bundles for candidaemia: the impact of compliance on clinical outcomes. J AntimicrobChemother. 2015 Feb;70(2):587-93. http://www.ncbi.nlm.nih.gov/pubmed/25326087

[vi] Amphotericin B, IV: Rex JH, Bennett JE, Sugar AM, Pappas PG, van der Horst CM, Edwards JE, Washburn RG, Scheld WM, Karchmer AW, Dine AP, et al. A randomized trial comparing fluconazole with amphotericin B for the treatment of candidemia in patients without neutropenia.Candidemia Study Group and the National Institute. N EnglJ Med. 1994 Nov 17;331(20):1325-30. http://www.ncbi.nlm.nih.gov/pubmed/7935701

Amphotericin B, IV: Phillips P, Shafran S, Garber G, Rotstein C, Smaill F, Fong I, Salit I, Miller M, Williams K, Conly JM, Singer J, Ioannou S. Multicenter randomized trial of fluconazole versus amphotericin B for treatment of candidemia in non-neutropenic patients. Canadian Candidemia Study Group. Eur J ClinMicrobiol Infect Dis. 1997 May;16(5):337-45. http://www.ncbi.nlm.nih.gov/pubmed/9228472

Amphotericin B, IV: Anaissie EJ, Darouiche RO, Abi-Said D, Uzun O, Mera J, Gentry LO, Williams T, Kontoyiannis DP, Karl CL, Bodey GP. Management of invasive candidal infections: results of a prospective, randomized, multicenter study of fluconazole versus amphotericin B and review of the literature. Clin Infect Dis. 1996 Nov;23(5):964-72. http://www.ncbi.nlm.nih.gov/pubmed/8922787

Amphotericin B, IV: Takesue Y, Ueda T, Mikamo H, Oda S, Takakura S, Kitagawa Y, Kohno S; ACTIONs Project. Management bundles for candidaemia: the impact of compliance on clinical outcomes. J AntimicrobChemother. 2015 Feb;70(2):587-93. http://www.ncbi.nlm.nih.gov/pubmed/25326087

Amphotericin B, IV: WHO. Diagnosis, Prevention and Management of Cryptococcal disease in HIV- infected Adults, Adolescents and children – 2011. Geneva: World Health Organization; 2011.http://www.who.int/en/

Amphotericin B, IV: Atsmon J, Dolev E. Drug-induced hypomagnesaemia : scope and management. Drug Saf. 2005;28(9):763-88. http://www.ncbi.nlm.nih.gov/pubmed/16119971

Amphotericin B, IV: WHO. Rapid advice: diagnosis, prevention and management of cryptococcal disease in HIV-infected adults, adolescents and children. 2011 [Online][Accessed June 2015] http://www.ncbi.nlm.nih.gov/books/NBK299520/pdf/Bookshelf_NBK299520.pdf

[vii] Fluconazole, oral: Rex JH, Pappas PG, Karchmer AW. A randomized and blinded multicenter trial of high-dose fluconazole plus placebo versus fluconazole plus amphotericin B as therapy for candidemia and its consequences in nonneutropenic subjects. The National Institute of Allergy and Infectious Diseases Mycoses Study Group.Clin Infect Dis 2001; 36: 1221–8.http://www.ncbi.nlm.nih.gov/pubmed/12746765

Fluconazole, oral: Edwards JE Jr, Bodey GP, Bowden RA, Büchner T, de Pauw BE, Filler SG, GhannoumMA, Glauser M, Herbrecht R, Kauffman CA, Kohno S, Martino P, Meunier F, Mori T, Pfaller MA, Rex JH, Rogers TR, Rubin RH, Solomkin J, Viscoli C, Walsh TJ, White M. International Conference for the Development of a Consensus on the Management and Prevention of Severe Candidal Infections. Clin Infect Dis. 1997 Jul;25(1):43-59. Review.http://www.ncbi.nlm.nih.gov/pubmed/9243032 Fluconazole, oral: Andes D, van Ogtrop H. Characterization and quantitation of the pharmacodynamics of fluconazole in a neutropenic murine disseminated candidiasis infection model. Antimicrob Agents Chemother 1999; 43:2116–20.http://www.ncbi.nlm.nih.gov/pubmed/10471550
SAMF 14th edition pg 327

[viii] Echinocandins (specialist motivation): National Institute for Communicable Diseases. The GERMS-SA Annual Report 2016. https://www.nicd.ac.za/wp-content/uploads/2017/03/GERMS-SA-AR-2016-FINAL.pdf

Echinocandins (specialist motivation): National Department of Health: Essential Drugs Programme. Tertiary and Quaternary EML, June 2022. https://www.knowledgehub.org.za/elibrary/hospital-level-tertiary-and-quaternary-essential-medicines-list

[ix] Cefazolin, IV: McDanel JS, Perencevich EN, Diekema DJ, Herwaldt LA, Smith TC, ChrischillesEA, Dawson JD, Jiang L, Goto M, Schweizer ML. Comparative effectiveness of beta-lactams versus vancomycin for treatment of methicillin-susceptible Staphylococcus aureus bloodstream infections among 122 hospitals. Clin Infect Dis. 2015 Aug 1;61(3):361-7.https://www.ncbi.nlm.nih.gov/pubmed/25900170

[x] Flucloxacillin, oral (dose): South African Medicines Formulary. 14th Edition. Division of Clinical Pharmacology. University of Cape Town. 2022.

[xi] Ertapenem, IV (severe penicillin allergy & confirmed Gram negative culture): An MM, Zou Z, Shen H, Zhang JD, Chen ML, Liu P, Wang R, Jiang YY. Ertapenem versus piperacillin/tazobactam for the treatment of complicated infections: a meta-analysis of randomized controlled trials. BMC Infect Dis. 2009 Dec 2;9:193. https://www.ncbi.nlm.nih.gov/pubmed/19951447

Ertapenem (severe penicillin allergy & confirmed Gram negative culture): NICD AMR surveillance for ESKAPE, 1 January 2016 to 31 December 2016.

[xii] Empiric antibiotic therapy (surgical wound infections): Stevens DL, Bisno AL, Chambers HF, Dellinger EP, Goldstein EJ, Gorbach SL, Hirschmann JV, Kaplan SL, Montoya JG, Wade JC. Practice guidelines for the diagnosis and management of skin and soft tissue infections: 2014 update by the Infectious Diseases Society of America. Clin Infect Dis. 2014 Jul 15;59(2):e10-52. Erratum in: Clin Infect Dis. 2015 May 1;60(9):1448. Dosage error in article text.http://www.ncbi.nlm.nih.gov/pubmed/24973422

[xiii] Empiric antibiotic therapy (surgical wound infections): Stevens DL, Bisno AL, Chambers HF, Dellinger EP, Goldstein EJ, Gorbach SL, Hirschmann JV, Kaplan SL, Montoya JG, Wade JC. Practice guidelines for the diagnosis and management of skin and soft tissue infections: 2014 update by the Infectious Diseases Society of America. Clin Infect Dis. 2014 Jul 15;59(2):e10-52. Erratum in: Clin Infect Dis. 2015 May 1;60(9):1448. Dosage error in article text.http://www.ncbi.nlm.nih.gov/pubmed/24973422

Ceftriaxone, IV (Surgery on female uro-genital tract/ open GIT surgery): Stevens DL, Bisno AL, Chambers HF, Dellinger EP, Goldstein EJ, Gorbach SL, Hirschmann JV, Kaplan SL, Montoya JG, Wade JC. Practice guidelines for the diagnosis and management of skin and soft tissue infections: 2014 update by the Infectious Diseases Society of America. Clin Infect Dis. 2014 Jul 15;59(2):e10-52. Erratum in: Clin Infect Dis. 2015 May 1;60(9):1448. Dosage error in article text.http://www.ncbi.nlm.nih.gov/pubmed/24973422

Metronidazole, IV (Surgery on female uro-genital tract/ open GIT surgery): Stevens DL, Bisno AL, Chambers HF, Dellinger EP, Goldstein EJ, Gorbach SL, Hirschmann JV, Kaplan SL, Montoya JG, Wade JC. Practice guidelines for the diagnosis and management of skin and soft tissue infections: 2014 update by the Infectious Diseases Society of America. Clin Infect Dis. 2014 Jul 15;59(2):e10-52. Erratum in: Clin Infect Dis. 2015 May 1;60(9):1448. Dosage error in article text.http://www.ncbi.nlm.nih.gov/pubmed/24973422

[xiv] Vancomycin, IV: Reardon J, Lau TT, Ensom MH. Vancomycin loading doses: a systematic review. Ann Pharmacother. 2015 May;49(5):557-65. http://www.ncbi.nlm.nih.gov/pubmed/25712445

Vancomycin, IV: Rybak M, Lomaestro B, Rotschafer JC, Moellering R Jr, Craig W, Billeter M, Dalovisio JR, Levine DP. Therapeutic monitoring of vancomycin in adult patients: a consensus review of the American Society of Health-System Pharmacists, the Infectious Diseases Society of America, and the Society of Infectious Diseases Pharmacists. Am J Health Syst Pharm. 2009 Jan 1;66(1):82-98. Erratum in: Am J Health Syst Pharm. 2009 May 15;66(10):887. http://www.ncbi.nlm.nih.gov/pubmed/19106348

Vancomycin, IV: South African Medicines Formulary. 14th Edition. Division of Clinical Pharmacology. University of Cape Town. 2022.

[xv] Criterion for empiric antibiotic therapy for MDR-HAP and MDR-VAP: Meta-analysis in guideline - Kalil AC, Metersky ML, Klompas M, Muscedere J, Sweeney DA, Palmer LB et al. Management of Adults With Hospital-acquired and Ventilator-associated Pneumonia: 2016 Clinical Practice Guidelines by the Infectious Diseases Society of America and the American Thoracic Society. Clin Infect Dis. 2016 Sep 1;63(5):e61-e111. https://www.ncbi.nlm.nih.gov/pubmed/27418577

[xvi] Duration of antibiotic therapy (7 days for VAP): Pugh R, Grant C, Cooke RP, Dempsey G. Short-course versus prolonged-course antibiotic therapy for hospital-acquired pneumonia in critically ill adults. Cochrane Database Syst Rev. 2015 Aug 24;2015(8):CD007577. https://pubmed.ncbi.nlm.nih.gov/26301604/

Duration of antibiotic therapy (7 days for VAP): Dimopoulos G, Poulakou G, Pneumatikos IA, Armaganidis A,

Kollef MH, Matthaiou DK. Short- vs long-duration antibiotic regimens for ventilator-associated pneumonia: a systematic review and meta-analysis. Chest. 2013 Dec;144(6):1759-1767. https://pubmed.ncbi.nlm.nih.gov/23788274/

Duration of antibiotic therapy (7 days for VAP/HAP): Kalil AC, Metersky ML, Klompas M, Muscedere J, Sweeney DA, Palmer LB, Napolitano LM, et al. Management of Adults With Hospital-acquired and Ventilator-associated Pneumonia: 2016 Clinical Practice Guidelines by the Infectious Diseases Society of America and the American Thoracic Society. Clin Infect Dis. 2016 Sep 1;63(5):e61-e111. doi: 10.1093/cid/ciw353. Epub 2016 Jul 14. Erratum in: Clin Infect Dis. 2017 May 1;64(9):1298. Erratum in: Clin Infect Dis. 2017 Oct 15;65(8):1435. Erratum in: Clin Infect Dis. 2017 Nov 29;65(12):2161. https://pubmed.ncbi.nlm.nih.gov/27418577/

[xvii] Piperacillin/tazobactam and amikacin: Nau R, Kinzig-Schippers M, Sörgel F, Schinschke S, Rössing R, Müller C, Kolenda H, Prange HW. Kinetics of piperacillin and tazobactam in ventricular cerebrospinal fluid of hydrocephalic patients.Antimicrob Agents Chemother. 1997 May;41(5):987-91.http://www.ncbi.nlm.nih.gov/pubmed/9145857

[xviii] Cefepime, IV (2 g): NICD AMR surveillance for ESKAPE, 1 January 2016 to 31 December 2016.

Cefepime, IV (2 g): South African Medicines Formulary. 14th Edition. Division of Clinical Pharmacology. University of Cape Town. 2022.

[xix] Imipenem, IV: South African Medicines Formulary. 14th Edition. Division of Clinical Pharmacology. University of Cape Town. 2022.

Imipenem, IV: NICD AMR surveillance for ESKAPE, 1 January 2016 to 31 December 2016.

[xx] Carbapenem (use of imipenem/cilastin and meropenem): South African Medicines Formulary. 14th Edition. Division of Clinical Pharmacology. University of Cape Town. 2022.

Cannon JP, Lee TA, Clark NM, Setlak P, Grim SA. The risk of seizures among the carbapenems: a meta-analysis. J Antimicrob Chemother. 2014 Aug;69(8):2043-55. doi: 10.1093/jac/dku111. Epub 2014 Apr 16. PMID: 24744302.

[xxi] Ciprofloxacin, oral: NHLS/NICD Communicable Diseases Surveillance Bulletin, April 2015 (Volume 13. No 1). http://www.nicd.ac.za/

[xxii] Pneumococcal vaccine (23 valent polysaccharide): ACIP Practice Guidelines - CDC. Morbidity and Mortality Weekly Report, October 12, 2012, Vol 61, No 40.http://www.cdc.gov/mmwr/preview/mmwrhtml/mm6140a4.htm?s_cid=mm6140a4_w

[xxiii] Gentamicin: SAMF 14th Edition. Division of Clinical Pharmacology. University of Cape Town. 2022.

[xxiv] Management of Covid-19: National Institute for Communicable diseases. Clinical management of suspected or confirmed Covid-19 disease Version 5 (24th August 2020). https://www.nicd.ac.za/diseases-a-z-index/covid-19/covid-19-guidelines/clinical-management-of-suspected-or-confirmed-covid-19-disease/

Management of Covid-19 in pregnancy: Royal College of Obstetricians & Gynaecologists. Coronavirus (COVID-19) Infection in Pregnancy Guidelines, 24 October 2020. https://www.rcog.org.uk/globalassets/documents/guidelines/2020-10-14-coronavirus-covid-19-infection-in-pregnancy-v12.pdf

[xxv] Heparin thromboprophylaxis: National Department of Health: Affordable Medicines, EDP-NEMLC COVID-19. Rapid review: A review of the optimal dose of either unfractionated heparin or low molecular weight heparin in the prevention of venous thromboembolism in patients with severe COVID-19: evidence review of the clinical benefit and harm, 13 September 2020. http://www.health.gov.za/

Heparin thromboprophylaxis: Middeldorp S, Coppens M, van Haaps TF, et al. Incidence of venous thromboembolism in hospitalized patients with COVID-19. J Thromb Haemost. 2020; https://doi.org/10.1111/jth.14888

[xxvi] Heparin – indications for therapeutic doses: National Institute for Communicable diseases. Clinical management of suspected or confirmed Covid-19 disease Version 5 (24th August 2020). https://www.nicd.ac.za/diseases-a-z-index/covid-19/covid-19-guidelines/clinical-management-of-suspected-or-confirmed-covid-19-disease/

[xxvii] Corticosteroid therapy: National Department of Health: Affordable Medicines, EDP-NEMLC COVID-19. Rapid review: Corticosteroids for COVID-19: evidence review of the clinical benefit and harm, 24 October 2020. http://www.health.gov.za/

Corticosteroid therapy: WHO Rapid Evidence Appraisal for COVID-19 Therapies (REACT) Working Group, Sterne JAC, Murthy S, Diaz JV et al. Association Between Administration of Systemic Corticosteroids and Mortality Among Critically Ill Patients With COVID-19: A Meta-analysis. JAMA. 2020 Sep 2;324(13):1–13. https://pubmed.ncbi.nlm.nih.gov/32876694/

[xxviii] Corticosteroid therapy (pregnancy): National Department of Health: Affordable Medicines, EDP-NEMLC COVID-19. Rapid review: Corticosteroids for COVID-19: evidence review of the clinical benefit and harm, 24 October 2020. http://www.health.gov.za/

Corticosteroid therapy (pregnancy): WHO Rapid Evidence Appraisal for COVID-19 Therapies (REACT) Working Group, Sterne JAC, Murthy S, Diaz JV et al. Association Between Administration of Systemic Corticosteroids and Mortality Among Critically Ill Patients With COVID-19: A Meta-analysis. JAMA. 2020 Sep 2;324(13):1–13. https://pubmed.ncbi.nlm.nih.gov/32876694/

[xxix] Albendazole (with meals) : Rigter IM, Schipper HG, Koopmans RP, van Kan HJ, Frijlink HW, Kager PA, Guchelaar HJ. Relative bioavailability of three newly developed albendazole formulations: a randomized crossover

study with healthy volunteers. Antimicrob Agents Chemother. 2004 Mar;48(3):1051-4.http://www.ncbi.nlm.nih.gov/pubmed/14982808.
Package Insert. Wormadole 400mg chewable tablets. Shanur Healthcare (Pty) Ltd. Date of revision of text 22 January 2024.

[xxx] Albendazole plus PAIR surgery: Smego RA Jr, Bhatti S, Khaliq AA, Beg MA. Percutaneous aspiration-injection-reaspiration drainage plus albendazole or mebendazole for hepatic cystic echinococcosis: a meta-analysis. Clin Infect Dis. 2003 Oct 15;37(8):1073-83. http://www.ncbi.nlm.nih.gov/pubmed/14523772

[xxxi] Artesunate, IV: Artesunate, parenteral: Sinclair D, Donegan S, Isba R, Lalloo DG. Artesunate versus quinine for treating severe malaria. Cochrane Database Syst Rev. 2012 Jun 13;6:CD005967.http://www.ncbi.nlm.nih.gov/pubmed/22696354

[xxxii] Prednisone, oral: Grandière-Pérez L, Ansart S, Paris L, Faussart A, Jaureguiberry S, Grivois JP,Klement E, Bricaire F, Danis M, Caumes E. Efficacy of praziquantel during the incubation and invasive phase of Schistosoma haematobium schistosomiasis in 18 travelers. Am J Trop Med Hyg. 2006 May;74(5):814-8. https://www.ncbi.nlm.nih.gov/pubmed/16687686

[xxxiii] Praziquantel, oral: Grandière-Pérez L, Ansart S, Paris L, Faussart A, Jaureguiberry S, Grivois JP,Klement E, Bricaire F, Danis M, Caumes E. Efficacy of praziquantel during the incubation and invasive phase of Schistosoma haematobium schistosomiasis in 18 travelers. Am J Trop Med Hyg. 2006 May;74(5):814-8. https://www.ncbi.nlm.nih.gov/pubmed/16687686

[xxxiv] Praziquantel, oral (repeat dose): Grandière-Pérez L, Ansart S, Paris L, Faussart A, Jaureguiberry S, Grivois JP,Klement E, Bricaire F, Danis M, Caumes E. Efficacy of praziquantel during the incubation and invasive phase of Schistosoma haematobium schistosomiasis in 18 travelers. Am J Trop Med Hyg. 2006 May;74(5):814-8. https://www.ncbi.nlm.nih.gov/pubmed/16687686

[xxxv] Diazepam, IV: Vassa NT, Doshi HV, Yajnik VH, Shah SS, Joshi KR, Patel SH. Comparative clinical trial of diazepam with other conventional drugs in tetanus. Postgrad Med J. 1974 Dec;50(590):755-8.http://www.ncbi.nlm.nih.gov/pubmed/4619836

Diazepam, IV: Wilson KC, Reardon C, Theodore AC, Farber HW. Propylene glycol toxicity: a severe iatrogenic illness in ICU patients receiving IV benzodiazepines: a case series and prospective, observational pilot study. Chest. 2005 Sep;128(3):1674-81.http://www.ncbi.nlm.nih.gov/pubmed/16162774

[xxxvi] Metronidazole, IV: World Health Organisation. Technical note: Current recommendations for treatment of tetanus during humanitarian emergencies, January 2010. https://www.who.int/diseasecontrol_emergencies/who_hse_gar_dce_2010_en.pdf

[xxxvii] Paracetamol (fever in tetanus): Lee BH, Inui D, Suh GY, Kim JY, Kwon JY, Park J, et al: Fever and Antipyretic in Critically ill patients Evaluation (FACE) Study Group. Association of body temperature and antipyretic treatments with mortality of critically ill patients with and without sepsis: multi-centered prospective observational study. Crit Care. 2012 Feb 28;16(1):R33. https://www.ncbi.nlm.nih.gov/pubmed/22373120

[xxxviii] Doxycycline, oral: Chapman AS, Bakken JS, Folk SM, Paddock CD, Bloch KC, Krusell A, et al: Tickborne Rickettsial Diseases Working Group; CDC. Diagnosis and management of tickborne rickettsial diseases: Rocky Mountain spotted fever, ehrlichioses, and anaplasmosis--United States: a practical guide for physicians and other health-care and public health professionals. MMWR Recomm Rep. 2006 Mar 31;55(RR-4):1-27. https://www.ncbi.nlm.nih.gov/pubmed/16572105

[xxxix] Doxycycline (pregnancy – tick bite fever): Frean J, Grayson W. South African Tick Bite Fever: An Overview. Dermatopathology (Basel). 2019 Jun 26;6(2):70-76. https://pubmed.ncbi.nlm.nih.gov/31700846/
Doxycycline (pregnancy – tick bite fever): Cross R, Ling C, Day NP, McGready R, Paris DH. Revisiting doxycycline in pregnancy and early childhood--time to rebuild its reputation? Expert Opin Drug Saf. 2016;15(3):367-82. https://pubmed.ncbi.nlm.nih.gov/26680308/
Doxycycline (pregnancy – tick bite fever): McGready R, Prakash JA, Benjamin SJ, Watthanaworawit W, Anantatat T, Tanganuchitcharnchai A, et al. Pregnancy outcome in relation to treatment of murine typhus and scrub typhus infection: a fever cohort and a case series analysis. PLoS Negl Trop Dis. 2014 Nov 20;8(11):e3327. https://pubmed.ncbi.nlm.nih.gov/25412503/
Doxycycline (pregnancy – tick bite fever): SAMF14th Edition. Division of Clinical Pharmacology. University of Cape Town, 2022.
Doxycycline (pregnancy – tick bite fever): Cooper WO, Hernandez-Diaz S, Arbogast PG, Dudley JA, Dyer SM, Gideon PS, et al. Antibiotics potentially used in response to bioterrorism and the risk of major congenital malformations. Paediatr Perinat Epidemiol. 2009 Jan;23(1):18-28. https://pubmed.ncbi.nlm.nih.gov/19228311/

[xl] Azithromycin, oral (pregnancy): Cascio A, Colomba C, Antinori S, Paterson DL, Titone L. Clarithromycin versus azithromycin in the treatment of Mediterranean spotted fever in children: a randomized controlled trial. Clin Infect Dis. 2002 Jan 15;34(2):154-8. http://www.ncbi.nlm.nih.gov/pubmed/11740701
Lee SC, Cheng YJ, Lin CH, Lei WT, Chang HY, Lee MD, Liu JM, Hsu RJ, Chiu NC, Chi H, Peng CC, Tsai TL, Lin CY. Comparative effectiveness of azithromycin for treating scrub typhus: A PRISMA-compliant systematic review and meta-analysis. Medicine (Baltimore). 2017 Sep;96(36):e7992. doi: 10.1097/MD.0000000000007992. PMID: 28885357; PMCID: PMC6392745.

[xli] Ciprofloxacin, IV: Raoult D, Drancourt M. Antimicrobial therapy of rickettsial diseases. Antimicrob Agents Chemother. 1991 Dec;35(12):2457-62. http://www.ncbi.nlm.nih.gov/pubmed/1810178

[xlii] Treatment failure > 48 hours requiring referral: Chapman AS, Bakken JS, Folk SM, Paddock CD, Bloch KC, Krusell A, et al: Tickborne Rickettsial Diseases Working Group; CDC. Diagnosis and management of tickborne rickettsial diseases: Rocky Mountain spotted fever, ehrlichioses, and anaplasmosis--United States: a practical guide for physicians and other health-care and public health professionals. MMWR Recomm Rep. 2006 Mar 31;55(RR-4):1-27. https://www.ncbi.nlm.nih.gov/pubmed/16572105

[xliii] Ceftriaxone, IV: Acharya G, Butler T, Ho M, Sharma PR, Tiwari M, Adhikari RK, Khagda JB, Pokhrel B, Pathak UN. Treatment of typhoid fever: randomized trial of a three-day course of ceftriaxone versus a fourteen-day course of chloramphenicol. Am J Trop Med Hyg. 1995 Feb;52(2):162-5. http://www.ncbi.nlm.nih.gov/pubmed/7872445

Ceftriaxone, IV: Smith MD, Duong NM, Hoa NT, Wain J, Ha HD, Diep TS, Day NP, Hien TT, White NJ. Comparison of ofloxacin and ceftriaxone for short-course treatment of enteric fever.Antimicrob Agents Chemother. 1994 Aug;38(8):1716-20. http://www.ncbi.nlm.nih.gov/pubmed/7986000

Ceftriaxone, IV: Wallace MR, Yousif AA, Mahroos GA, Mapes T, Threlfall EJ, Rowe B, Hyams KC. Ciprofloxacin versus ceftriaxone in the treatment of multiresistant typhoid fever. Eur J ClinMicrobiol Infect Dis. 1993 Dec;12(12):907-10. http://www.ncbi.nlm.nih.gov/pubmed/8187784

Ceftriaxone, IV: Islam A, Butler T, Kabir I, Alam NH. Treatment of typhoid fever with ceftriaxone for 5 days or chloramphenicol for 14 days: a randomized clinical trial. Antimicrob Agents Chemother. 1993 Aug;37(8):1572-5. http://www.ncbi.nlm.nih.gov/pubmed/8215265

Ceftriaxone, IV: Lasserre R, Sangalang RP, Santiago L. Three-day treatment of typhoid fever with two different doses of ceftriaxone, compared to 14-day therapy with chloramphenicol: a randomized trial. J AntimicrobChemother. 1991 Nov;28(5):765-72. http://www.ncbi.nlm.nih.gov/pubmed/1778879

Ceftriaxone, IV: Islam A, Butler T, Nath SK, Alam NH, Stoeckel K, Houser HB, Smith AL. Randomized treatment of patients with typhoid fever by using ceftriaxone or chloramphenicol. J Infect Dis. 1988 Oct;158(4):742-7. http://www.ncbi.nlm.nih.gov/pubmed/3171225

[xliv] Antiviral, oral (active against herpes zoster) therapeutic class: Tunbridge AJ et al; British Infection Society. Chickenpox in adults - clinical management. J Infect. 2008 Aug;57(2):95-102. https://pubmed.ncbi.nlm.nih.gov/18555533/

[xlv] Varicella-zoster immunoglobulin (VZIG), IM (indication of immunocompromised with no immunity): Centers for Disease Control and Prevention (CDC). Updated recommendations for use of VariZIG--United States, 2013. MMWR Morb Mortal Wkly Rep. 2013 Jul 19;62(28):574-6. https://pubmed.ncbi.nlm.nih.gov/23863705/
SAMF 14th edition, Varicella-zoster immunoglobulin monograph, pg 373.

[xlvi] Antivirals to treat herpes zoster (therapeutic class): Tunbridge AJ et al; British Infection Society. Chickenpox in adults - clinical management. J Infect. 2008 Aug;57(2):95-102. https://pubmed.ncbi.nlm.nih.gov/18555533/

[xlvii] Aciclovir, IV - dose adjustment in renal impairment: SAMF 14th Edition. Division of Clinical Pharmacology. University of Cape Town. 2022.

CHAPTER 10
HIV AND AIDS

Comprehensive guidelines are available for ART and the care of adults and children with HIV infection in the 2023 ART Clinical Guidelines for the Management of HIV in Adults, Pregnancy and Breastfeeding, Adolescents, Children, Infants and Neonates.[i]

10.1 ANTIRETROVIRAL THERAPY

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Antiretroviral therapy (ART) consists of combinations of antiretroviral medicines that are capable of suppressing HIV replication (defined as an undetectable viral load). Continued use of ART with a detectable viral load results in the development of resistance to some or all of the medicines in the regimen. High levels of adherence are essential for long-term success with ART.

The current recommended first-line ART regimen contains two nucleoside reverse transcriptase inhibitors (NRTIs) together with an integrase strand transfer inhibitor (InSTI) dolutegravir (DTG). Previously a non-nucleoside reverse transcriptase inhibitor (NNRTI), efavirenz or nevirapine, together with two NRTIs, were recommended for first-line ART. DTG is better tolerated than the NNRTIs and has a much higher barrier to the development of resistance.
DTG, together with two NRTIs, is now also recommended in a patient who has failed an NNRTI-based (formerly first-line) regimen. Previously a protease inhibitor (PI), together with two NRTIs, was recommended for second-line ART, but DTGis better tolerated than PIs. Switching people established on ART to the newer DTG-based ART regimens need to be carefully done to reduce the risk of the emergence of resistance (refer to National Department of Health HIV Guidelines and “Switching existing clients to DTG-containing regimens” section in Table 10.1: ART regimens).

ELIGIBILITY FOR ART

Eligibility to start ART:
All adults with confirmed HIV infection, irrespective of CD4 count or WHO clinical stage.

LoE: Ia[ii]

Immediate initiation:
ART should be initiated immediately in pregnancy and during breastfeeding.

LoE:IIa[iii]

Timing of ART initiation:

» Where a patient is willing and ready, ART should be initiated on the same day as HIV diagnosis, except in patients with TB or cryptococcal meningitis (see Timing of ART initiation below).

» In TB co-infection, start with TB treatment first, followed by ART initiation according to CD4 count (except TB meningitis – see below):
  - CD4 <50 cells/mm^3: initiate ART within 2 weeks of starting TB treatment.
  - CD4 ≥50 cells/mm^3: defer ART until 8 weeks after starting TB treatment, as this does not increase the risk of mortality and reduces the risk of deterioration due to immune reconstitution inflammatory syndrome (IRIS).

LoE:Ia[iv]

» In patients with TB meningitis (irrespective of CD4 count), defer ART until 8 weeks after initiating TB treatment.

LoE:IIIa[v]

» In patients with cryptococcal meningitis, defer ART until 4–6 weeks after starting antifungal treatment (earlier initiation has been shown to increase the risk of death).

LoE:IIIa[vi]

» In patients with positive cryptococcal antigen and no evidence for meningitis on LP, there is no need to delay. ART can be started immediately.

LoE:IVb[vii]

PSYCHOSOCIAL INDICATORS OF READINESS FOR ART

It is essential that patients have good insight into the need for long-term therapy and high levels of adherence. Pay careful attention to adherence planning. Encourage patients to disclose their HIV status to somebody to act as a treatment supporter. If this is not possible then the patient should join a support group.

Manage depression.

Active substance abuse/alcoholism is an impediment to adherence and, if possible, should be addressed prior to initiating ART.

LoE:IIIb[viii]

ART REGIMENS

INITIATING ART	
Treatment-naïve patients	Individuals ≥30kg: TDF + 3TC + DTG ("TLD") *LoE:IIa*[ix] **Note***:* DTG-based regimens are now recommended as first line ART in all women of child-bearing potential. *LoE:IIa*[x] Patients on rifampicin-based TB treatment: TDF + FTC + EFV **OR**

	TDF + 3TC + DTG *plus* additional dose of DTG 50 mg 12 hours later. The extra DTG dose can be stopped two weeks after completion of TB therapy. *LoE:IIIb*[xi] (Also see AH STG Section 6.6: HIV in pregnancy.)
Contraindications/ intolerance to DTG	TDF + 3TC/FTC + EFV
Contraindications to EFV and DTG	Start protease inhibitor-based regimen: TDF + 3TC/FTC + ATV/r *LoE:IIb*[xii] **Note:** if patient requires rifampicin-based TB treatment, substitute ATV/r with LPV/r 800/200 mg 12-hourly. **Note:** There is an increased risk of ALT/AST elevations and gastrointestinal disorders. LPV/r dose should be gradually titrated upward over 1-2 weeks (e.g. 600/150 mg and then 800/200 mg). The LPV/r can be switched back to ATV two weeks after completion of TB therapy.
Contraindication to TDF » eGFR <50 mL/minute.	If chronic hepatitis B coinfection and eGFR 30-50 ml/min: TAF + FTC + DTG. Other scenarios: ABC + 3TC + DTG *LoE:IIIb*[xiii]
Contraindication to TDF/TAF and ABC intolerance/hypersensitivity	AZT + 3TC with DTG
Note: In the unlikely scenario where there is intolerance/contraindication to all currently available NRTIs, the following alternative dual-therapy regimens may be used **after** consulting a specialist: • DTG + 3TC (if no resistance/intolerance to 3TC and VL <500 000 copies/mL) • EFV + LPV/r • DTG + LPV/r *LoE:IIb*[xiv]	

VIROLOGICAL FAILURE	
Management of viraemia on TLD	<u>If plasma VL >50 copies/mL:</u> » Address adherence, tolerability, medicine interactions & psychosocial factors. » Repeat VL test 3 months later. <u>If plasma VL remains > 50:</u> » Assess adherence, tolerability, medicine interactions & psychosocial factors again. » If on TLD <2 years, or persistent low-level viraemia (50-999 copies/mL), or adherence suboptimal, repeat VL at next scheduled visit (i.e. in 6 months' time). » If on TLD >2 years and ≥2 consecutive VL ≥1000 copies/mL (or 1 VL ≥1000 copies/mL plus CD4 <200 or opportunistic infection), discuss with an HIV expert* whether a resistance test is indicated (as a rule it is not, and efforts to resolve adherence issues should be intensified instead).
SWITCHING EXISTING CLIENTS TO DTG-CONTAINING REGIMENS	
Patient on: » **TDF/FTC/EFV** » **ABC/3TC/EFV (or NVP)** » **AZT/3TC/EFV (or NVP)** » **AZT/3TC/DTG** » **Any LPV/r- or ATV/r-containing regimen for <2 years** » **Any LPV/r- or ATV/r-containing regimen with latest VL <1000 copies/mL**	Switch to DTG-containing regimen regardless of VL result: TDF + 3TC + DTG ("TLD") If contraindications to DTG or TDF, use alternative regimen as for first line above. *LoE:IIb*[xv]
Patient on: » **ATV/r or LPV/r regimen for >2 years and ≥2 consecutive viral loads ≥1000 copies/mL**	If adherence >80%, discuss with an HIV expert* to authorise and interpret a resistance test before switching. If adherence < 80%, switch to DTG-containing regimen: TDF + 3TC + DTG ("TLD") If contraindications to DTG or TDF, use alternative regimen as for first line above. *LoE:IIb*[xvi]

CLIENTS WITH DTG RESISTANCE	
Any DTG resistance shown on genotype authorised by HIV expert	Discuss case with an HIV expert*. The regimen will be determined by an Expert Committee based on the pattern of resistant mutations and the prior history of antiretroviral exposure. Application for 3rd line using the standard motivation form may be required (available on request from TLART@health.gov.za or download from https://knowledgehub.health.gov.za/elibrary/third-line-antiretrovirals).
RIFAMPICIN-BASED TB TREATMENT	
Rifampicin-based TB treatment	If on DTG: Add DTG 50 mg 12 hours after TLD dose. *LoE:IIIb*[xvii] If on ATV/r: Switch ATV/r to LPV/r 800/200 mg 12 hourly (i.e. double dose). **Note:** There is an increased risk of ALT/AST elevations and gastrointestinal disorders. LPV/r dose should be gradually titrated upward over 1-2 weeks. The LPV/r can be switched back to ATV/r two weeks after completion of TB therapy.

ABC=Abacavir, ATV/r=Atazanavir/ritonavir, AZT=Zidovudine, 3TC=Lamivudine, DTG= Dolutegravir, EFV=Efavirenz FTC=Emtricitabine, LPV/r=Lopinavir/ritonavir, TDF=Tenofovir disoproxil fumarate TAF= Tenofovir alafenamide

Table 10.1: ART regimens

*For advice from an HIV expert, approach an HIV Hotline, an infectious disease specialist, or the Third Line ART committee.

HIV Hotlines:

» National HIV & TB Health Care Worker Hotline: **0800 212 506**

» Right to Care Paediatric, Adolescent and Adult HIV Helpline: **082 352 6642**

» KZN Paediatric Hotline: **0800 006 603**

Note:

» Always check hepatitis B surface antigen (HBsAg) before stopping TDF.

» If patient has chronic hepatitis B, stopping TDF may lead to a fatal hepatitis flare.

» Continue TDF if HBsAg positive.

Currently available ARV FDC preparations on contract:

- ABC 600 mg + 3TC 300 mg,
- TDF 300 mg + FTC 200 mg,
- AZT 300 mg + 3TC 150 mg,
- LPV 100 mg + ritonavir 25 mg,
- LPV 200 mg + ritonavir 50 mg,
- TDF 300 mg + FTC 200 mg + EFV 600 mg,
- TDF 300 mg + DTG 50 mg + 3TC 300 mg,
- ATV 300 mg + ritonavir 100mg,
- ABC 600 mg + 3TC 300 mg + DTG 50 mg.

Source: Contract circular HP13-2022ARV http://www.health.gov.za/

RE-INITIATING ART IN PATIENTS WHO HAVE INTERRUPTED TREATMENT

» Do VL, recommence ART regimen unless there is a clinical indication to defer ART, repeat VL at 3 months. Recommence previous regimen (unless patient would qualify for a switch to TLD anyway as per above, in which case start DTG-based regimen, e.g. TLD).

» If VL does not to decrease to <1000 copies/mL at 3 months, manage as per virological failure above.

LoE:IIIb[xviii]

ART: DOSING AND IMPORTANT ADVERSE EFFECTS

Generic name	Class	Usual dose	Renal adjusted dose	Important adverse drug reactions (ADRs) and timing
Tenofovir disoproxil fumarate (TDF)	NRTI	300 mg daily	Avoid in renal impairment (eGFR <50 mL/min)	» Acute kidney injury (rare - weeks to months). » Decline in eGFR (months to years). » Fanconi syndrome (rare – months to years). » Reduced bone mineral density (months to years).
Abacavir (ABC)	NRTI	600 mg daily	Dose adjustment not required	» Hypersensitivity reaction (1 to 6 weeks) fever, rash, constitutional symptoms, gastrointestinal symptoms and respiratory symptoms.
Zidovudine (AZT)	NRTI	300 mg 12 hourly	eGFR <10 mL/min: 300 mg daily	» Anaemia, neutropenia (weeks to months). » Gastro-intestinal upset. » Headache. » Myopathy (rare). » Hyperlactataemia / steatohepatitis (medium risk - months). » Lipoatrophy (months to years).

Lamivudine (3TC)	NRTI	300 mg daily (or 150 mg 12 hourly)	eGFR 10-30 mL/min: 150 mg daily eGFR <10 mL/min: 50 mg daily	» Anaemia due to pure red cell aplasia (rare).
Emtricitabine (FTC)	NRTI	200 mg daily	eGFR 15-29 mL/min: 200 mg every 3 days eGFR <15 mL/min: 200 mg every 4 days Note: FTC is not available as a single-ingredient formulation.	» Palmar hyperpigmentation. » Anaemia due to pure red cell aplasia (rare). *LoE:IVb*[xix]
Efavirenz (EFV)	NNRTI	600 mg at night	Dose adjustment not required	» Central nervous system symptoms: vivid dreams, problems with concentration, confusion, mood disturbance, psychosis (days to weeks). » Encephalopathy, often with cerebellar features (uncommon – months to years). *LoE:IVb*[xx] » Rash (1 to 6 weeks). » Hepatitis (weeks to months) » Gynaecomastia.
Tenofovir alafenamide (TAF)	NRTI	25 mg daily If co-formulated with FTC, avoid if eGFR <30 ml/min. If used as a single agent, avoid if eGFR <15 ml/min and not on haemodialysis.		» Acute kidney injury. » Fanconi syndrome. » Reduced bone mineral density.
Lopinavir/ ritonavir (LPV/r)	Boosted PI	400/100 mg 12 hourly **OR** 800/200 mg daily (only if PI-naïve)	Dose adjustment not required	» Gastrointestinal upset. » Dyslipidaemia (weeks). » Rash and/or Hepatitis (1 to 6 weeks).
Atazanavir/ ritonavir (ATV/r)	Boosted PI	ATV 300 mg with ritonavir 100 mg daily	Dose adjustment not required	» Unconjugated hyperbilirubinaemia (common, but benign). » Dyslipidaemia (low risk). » Hepatitis (rare - 1 to 6 weeks). » Renal stones (uncommon).

Dolutegravir (DTG)	InSTIs	50 mg once daily	Dose adjustment not required	» Hypersensitivity (rare, weeks). » Insomnia (common). » Headache (common). » Other neuropsychiatric symptoms. » Nausea, diarrhoea (common). » Hepatitis (uncommon). » Increase in serum creatinine (<30 mmol/L within the first few weeks of DTG initiation) due to inhibition of creatinine secretion by DTG; this is clinically insignificant as glomerular filtration rate is not reduced but will modestly affect eGFR which is determined using serum creatinine.

Table 10.2: Dosing and important adverse effects associated with ART
The time-onset information with respect to adverse drug reactions (ADRs) serves as an estimate. Patients may present with ADRs with the onset deviating from that indicated in the table.

LoE:IIIb[xxi]

ART: DRUG-DRUG INTERACTIONS

Information can be accessed from:

» https://www.hiv-druginteractionslite.org/checker.
» http://www.mic.uct.ac.za/ download the ARV/EML interaction checker.
» Package inserts.

ART INTERACTIONS WITH RIFAMPICIN AND RECOMMENDATIONS FOR ADMINISTRATION			
Class	**ARV**	**Interaction with rifampicin**	**Dose of ARV with rifampicin**
NRTI	3TC/FTC/ TDF/ AZT/ABC	No clinically significant pharmacokinetic interactions.	No dose adjustment required.
NNRTI	EFV	Non-significant change (EFV concentrations may increase in patients who are genetic slow metabolisers of EFV and are on isoniazid which also inhibits EFV metabolism).	No dose adjustment required (600 mg at night).
PI	LPV/r	LPV plasma concentrations significantly decreased.	Double the dose of LPV/r to 800/200 mg 12 hourly. **Note:** There is an increased risk of ALT/AST elevations and gastrointestinal disorders. Dose should be gradually titrated upward over 1-2 weeks. Adjusted dose should be continued for 2 weeks after rifampicin is stopped.
	All other PIs	Marked reduction in PI concentrations.	Do not prescribe concomitantly – replace rifampicin with rifabutin 150 mg daily (see monitoring instructions below).
InSTI	DTG	Significant reduction in	Dose increased to 50 mg 12 hourly*.

		concentration of DTG.	

Table 10.3: ART interactions with rifampicin and dose-adjustment recommendations.

LoE:IIIb[xxii]

In patients on atazanavir or darunavir, or if double dose LPV/r is not tolerated, replace rifampicin with:

- Rifabutin, oral, 150 mg daily.
  - Monitor FBC monthly for anaemia and neutropenia.
  - Monitor clinically for symptoms of uveitis (e.g. pain, photophobia, variable loss of vision, circumcilliary injection, a miotic pupil) – immediately stop rifabutin pending ophthalmology opinion.

LoE:IIIb[xxiii]

DRUG INTERACTIONS WITH DOLUTEGRAVIR		
Interacting medicine	**Effect of co-administration**	**Recommendation**
Preparations containing polyvalent cations (Mg^{2+}, Ca^{2+}, Fe^{2+}, Al^{3+}, Zn^{2+}) Antacids Sucralfate Mineral supplements	Significant reduction in concentration of DTG	Magnesium- and aluminium-containing preparations should be taken 6 hours before or 2 hours after DTG. Calcium- and iron- containing preparations can be taken concomitantly with DTG when administered with food. **Note:** Iron and calcium should be taken at least 4 hours apart from one another.
Anticonvulsants: Carbamazepine Phenobarbital Phenytoin	Significant reduction in concentration of DTG	Avoid co-administration if possible. Consider valproate or lamotrigine. *For carbamazepine:* Double DTG dose to 50 mg 12 hourly.
Metformin	May increase metformin concentration	*Metformin initiation:* Initiate metformin at a low dose (500-1000mg total daily dose), titrating up as needed. Do not exceed 2 g daily. *DTG initiation:* If patient stabilised on metformin dose ≤2 g daily, retain metformin dose and monitor for side effects. If patient stabilised on >2 g daily, reduce dose of metformin to ≤2 g daily and monitor. *Patients with renal impairment:* Close monitoring of renal function required. Do not co-prescribe if eGFR <30 mL/min. See Appendix II for further guidance on patients with renal impairment.
Rifampicin	Significant reduction in concentration of DTG	Double DTG dose to 50 mg 12 hourly.

Table 10.4: Drug interactions with DTG

LoE:IIIb[xxiv]

DRUG INTERACTIONS WITH BOOSTED PIs		
Interacting medicine	**Effect of co-administration**	**Recommendation**
Substrates of cytochrome P450 3A4 (e.g. most statins, calcium channel blockers, most SSRIs, most benzodiazepines)	Significant increase in levels of *CYP3A4* substrates	Avoid co-administration or use lower doses of *CYP3A4* substrates (always consult interaction resources).
Anticonvulsants: Carbamazepine Phenobarbital Phenytoin	Significant reduction in concentration of PI	Avoid co-administration. Consider valproate or lamotrigine.
Proton pump inhibitors	Significant reduction in ATV levels	Avoid co-administration. *LoE:IIIb*[xxv]
Rifampicin	Significant reduction in levels of PI	Double LPV/r dose. Avoid co-administration of other PIs (replace rifampicin with rifabutin).

Table 10.5: Drug interactions with boosted PIs

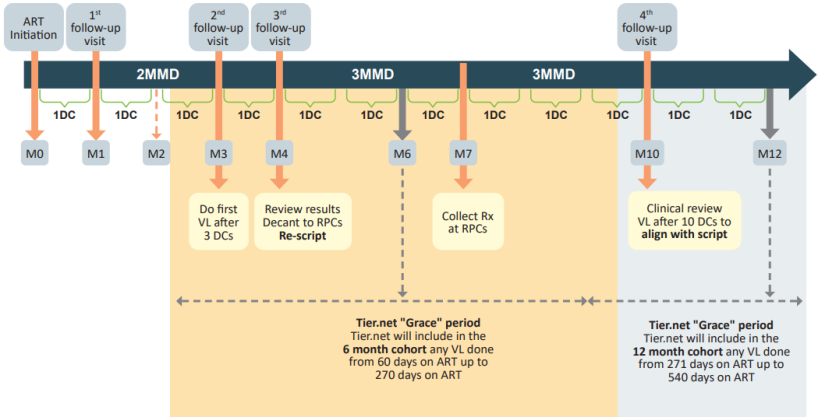
MONITORING ON ART	
Baseline evaluation	» Confirm HIV positive result with second test. » WHO staging. » Check CD4 count. *LoE:IVb*[xxvi] » If CD4 <200 cells/mm^3: – Check cryptococcal antigen (if positive, perform LP regardless of whether symptoms are present or not). – Initiate cotrimoxazole prophylaxis (see Section 10.2.2: Cotrimoxazole prophylaxis). – Reflex CrAg testing is done on the CD4 sample if CD4 <100 cells/mm^3. If patient's CD4 is 100-199, a serum CrAg test must be ordered separately. » Screen for pregnancy or ask if planning to conceive. » Screen for mental health, STIs and NCDs. » Screen for TB using the WHO screening questionnaire (any one of cough, fever, night sweats, or weight loss). » Sputum TB-NAAT* in all who can produce sputum, regardless of symptoms. » Urine LAM for inpatients or outpatients who are symptomatic if CD4 <200, or advanced HIV disease or current serious illness. » If planning to use TDF: check creatinine (avoid TDF if eGFR <50 mL/minute). » Haemoglobin *LoE:IIIb*[xxvii] » Check HBsAg (if positive, TDF should form part of the regimen). » Cervical cancer screening.

	*TB-NAAT: TB Nucleic Acid Amplification Tests (e.g. GeneXpert Ultra MTB/RIF). *LoE:IIb*[xxviii]
On ART	» Monitoring schedule has been adapted to minimise the number of visits required per annum. » VL at 3 and 10 months after initiating ART and every 12 months thereafter, if virologically suppressed. Align timing with client's scripting cycle. » CD4 at 10 months after initiating ART (align with VL). Stop CD4 count monitoring when >200 cells/mm^3 and virologically suppressed. If virological or clinical failure occurs, or if client returns >90 days after missing an appointment, then a CD4 count should be done as cotrimoxazole may need to be commenced/ recommenced. Repeat CD4 count every 6 months if VL remains ≥1000 copies/mL. » If on TDF: creatinine at month 3, month 10, and every 12 months thereafter. Align with VL monitoring schedule. » If on AZT: FBC and differential count at 1 and 3 months after initiating AZT, then only if clinically indicated. » ALT if symptoms of hepatitis develop. » If on a protease inhibitor (PI): cholesterol and triglycerides at 3 months after initiating PI. If above acceptable range, do fasting cholesterol and TGs and if still above acceptable range, obtain expert advice.

Table 10.6: Monitoring on ART

HIV VIRAL LOAD MONITORING SCHEDULE

Routine VL monitoring	Intervention	Comments
First VL after ART initiation	Do 1st VL after **3 dispensing cycles**	• Allows for earlier detection of factors influencing viral suppression • Allows for earlier decanting for suppressed clients to minimise visits and promote continued engagement in care • This VL will form part of the **6 month VL completion cohort** in Tier.net
Second routine VL after ART initiation (in clients who remain virally suppressed)	This VL can be done from **10 dispensing cycles** but should be aligned with the clients scripting cycle	• This VL will form part of the **12 month VL completion cohort** in Tier.net
Third routine VL after ART initiation (in clients who remain virally suppressed)	This VL can be done **from 22 dispensing cycles**, but should be aligned with the clients scripting cycle	• This VL will form part of the 24 month **VL completion cohort** in Tier.net
Fourth and all subsequent VLs	VLs will be taken at intervals of 12 dispensing cycles for all clients who remain virally suppressed	
The timing of dispensing cycles, follow-up visits, and VL monitoring is illustrated in the diagram below		



- For the 1st VL taken after 3 dispensing cycles, clients should be requested to return to the facility one DC later to review results and so that the client can be assessed for RPCs eligibility.
- For all subsequent VL monitoring (and other routine monitoring investigation) in clinically well clients: Clients should be rescripted at the same visit that their VL is taken. Clients should not be required to come back to the facility the following month for VL result review prior to rescript. Rather, recall to the facility only those clients with an elevated VL or other abnormal result.
- Facilities should ensure that results management processes are in place to ensure that results are reviewed by a clinician, that abnormal results are identified, and the client is appropriately actioned. The NHLS Results for Action (RfA) reports are a useful tool to facilitate the review of results.

! Breastfeeding women should have their VL monitored every 6 months starting from the time of delivery

DC: Dispensing cycle; MMD: Multi-month dispensing; RPCs: Repeat prescription collection strategies

Figure 10.1: Incorporated from the NDoH 2023 ART Clinical Guidelines for the Management of HIV in Adults, Pregnancy and Breastfeeding, Adolescents, Children, Infants and Neonates.

10.1.1 MANAGEMENT OF SELECTED ANTIRETROVIRAL ADVERSE DRUG REACTIONS

Dyslipidaemia E78.0-5 + (Y41.5 + B24)
The protease inhibitors can cause significant dyslipidaemia. Fasting lipids should be done 3 months after starting protease inhibitors. LPV/r is associated with a higher risk of dyslipidaemia (especially hypertriglyceridaemia) than ATV/r.

Patients on LPV/r with the following should switch to ATV/r and repeat the fasting lipids in three months:
» triglycerides >10 mmol/L,
» total cholesterol >6 mmol/L with a high risk (i.e. >20% risk of developing a CVD event in 10 years).

Patients with persistent dyslipidaemia despite switching to ATV/r may need lipid lowering therapy. Criteria for initiating lipid lowering therapy are the same as for HIV seronegative patients. (See Section 3.1: Ischaemic heart disease and atherosclerosis, prevention.)

Many statins (including simvastatin) cannot be used with protease inhibitors, as protease inhibitors inhibit the metabolism of the statin resulting in extremely high blood levels.

Patients, who fail to respond to lifestyle modification and have hypertriglyceridemia >10 mmol/L, treat with a fibric acid derivative, e.g.:
- Bezafibrate, oral, 400 mg at night.

OR
If LDL cholesterol is raised (see Section 3.1: Ischaemic heart disease and atherosclerosis, prevention):
- Atorvastatin, oral, 10 mg daily (do not exceed this dose due to a drug interaction with PIs).

Anaemia and neutropenia D64.9/D70 + (Y41.5 + B24)
AZT causes macrocytosis and can cause anaemia and neutropenia (note that it does not cause thrombocytopenia). AZT does not need to be stopped with mild anaemia and/or neutropenia, but must be stopped and replaced with an alternative medication if:
» anaemia is symptomatic,
» anaemia is severe (Hb <8.0 g/dL), or
» the neutrophil count is below 0.75×10^9/L.
Lamivudine and emtricitabine can cause pure red cell aplasia, but this is rare.

Hypersensitivity L27.0-1 + (Y41.5 + B24)
Note that pre-existing dermatological conditions (especially papulopruritic eruptions and acne) may worsen after commencing ART due to immune reconstitution inflammatory syndrome; see Section 10.1.2: Immune

reconstitution inflammatory syndrome (IRIS)) – this is not a hypersensitivity reaction and ART should be continued.

Other medicines, notably cotrimoxazole, can also cause hypersensitivity.

Hypersensitivity rashes occur commonly in the 8-week period after starting EFV. NNRTI-associated rashes can be severe and life-threatening.

If any of the following features occur when a patient is on EFV, then EFV must be permanently discontinued:
» Blistering.
» Lesions affecting mucous membranes (mouth, eyes, or genitals).
» Fever.

Patients with lesions affecting the mucous membranes, or with significant blistering, likely have Stevens Johnson syndrome or toxic epidermal necrolysis, and will require admission.
With mild rashes EFV can be continued with careful observation and the rash will often subside.
If rash worsens or does not improve within a week discontinue EFV.
DTG can cause systemic hypersensitivity syndrome with rash, but this is very uncommon. DTG should be permanently discontinued if this occurs.
ABC can cause a rash as part of a systemic hypersensitivity reaction, which is confined to people who are *HLA-B*5701* positive. ABC should be permanently discontinued if this occurs. *LoE:IVb*[xxix]

Hyperlactataemia E87.2 + (Y41.5 + B24)
Symptomatic hyperlactataemia occurs due to mitochondrial toxicity of NRTIs. The estimated risk of symptomatic hyperlactataemia differs among the NRTIs, with zidovudine having moderate risk and the other NRTIs very low risk.

Risk factors for hyperlactataemia include:
» females,
» obesity,
» prolonged use of NRTIs (> 3 months), or
» development of NRTI-induced fatty liver.

Clinical symptoms of hyperlactataemia are non-specific and may include:
» nausea
» vomiting
» abdominal pain
» weight loss
» malaise
» tachycardia
» liver dysfunction (due to steatosis)

A high index of suspicion is necessary. Send blood for lactate levels (check with your local laboratory for specimen requirements for lactate). Alternatively, point of care finger prick lactate monitoring can be done. Check the serum bicarbonate level if lactate is elevated to confirm metabolic acidosis.
Patients with mild hyperlactataemia (lactate 2.5–5 mmol/L):

Alter therapy, selecting NRTIs that are less associated with hyperlactataemia.
Note: The resolution of hyperlactataemia may take a few months.

Patients with lactate levels > 5 mmol/L:
» Stop the ART temporarily.
» Consult with an HIV specialist regarding the future ART plan.
» Admission to a high care unit is recommended in patients with acidosis.

Lactic acidosis carries a poor prognosis. Treatment is largely supportive. It is essential to exclude other causes of lactic acidosis, especially sepsis. High dose vitamin B, especially riboflavin and thiamine, may have a role in therapy.

Hepatotoxicity K71.9 + (Y41.5 + B24)
All currently available antiretrovirals are potentially hepatotoxic. EFV has the highest risk. NRTIs uncommonly cause acute hepatitis, but may result in steatohepatitis after prolonged use, which manifests with mildly elevated liver enzymes, affecting GGT and alkaline phosphatase more than the transaminases, and ALT more than AST. Patients on atazanavir may develop jaundice due an unconjugated hyperbilirubinaemia, which is not accompanied by liver injury. This is a cosmetic issue and the atazanavir can be substituted if the patient is unable to tolerate the jaundice. However, all protease inhibitors can rarely cause hepatitis, so it is important to exclude this in patients developing jaundice on ATV/r. DTG can cause a hepatitis, but this is rare.

Other potentially hepatotoxic medicines prescribed in PLHIV include anti-tuberculous therapy, fluconazole and cotrimoxazole. Cotrimoxazole, amoxicillin/clavulanate, and macrolides may cause cholestatic hepatitis that may take months to resolve.

The exclusion of viral hepatitis is important in the work-up of drug-induced liver injury (DILI). Testing for hepatitis A, B and C should be undertaken. Hepatitis B is common, and flares of viral hepatitis may occur after ART initiation (i.e. IRIS). Furthermore, life threatening flares may occur when antiretrovirals that are also active against hepatitis B (i.e. TDF, 3TC and FTC) are withdrawn.

Other potential causes include disseminated TB, IRIS, alcohol, alternative remedies, fatty liver, sepsis and HIV cholangiopathy.

Investigations:
» Request an ALT.
» Request viral hepatitis screen, full liver function tests and INR in patients with any of the following criteria:
    - ALT >5 x upper limit of normal (ULN).
    - Jaundice.
    - Other symptoms of hepatitis (e.g. right upper quadrant pain, nausea or vomiting).

» Perform a liver ultrasound if GGT or ALP are significantly elevated or if conjugated bilirubin is elevated, to exclude:
  - Extrahepatic biliary obstruction.
  - Fatty liver due to NRTIs.
  - Disseminated TB.

Management:

Upper Limit of Normal (ULN)	<2.5 x ULN	2.5 – 5 x ULN	> 5 x ULN
ALT	Repeat in 2 weeks	Repeat in 1 week	Stop ART

*Stop the relevant medicines at lower levels if symptoms of hepatitis (right upper quadrant pain, nausea / vomiting) or jaundice are present.

Table 10.7: Management of hepatotoxicity associated with ART

If ART is considered to be the cause, substitute ART as follows:
» If the hepatitis occurred on efavirenz, substitute with DTG or a boosted PI.
» If hepatitis occurred on PI, substitute with DTG.
» NRTI fatty liver – discontinue AZT (if relevant) and replace with safer NRTI (TDF or ABC) – if not on AZT and hepatitis is severe switch to NRTI-sparing regimen (see footnote in Table 10.1: ART regimens, located in Section 10.1: Antiretroviral therapy. Importantly, consult a specialist).

Hepatitis in patients on ART and anti-tuberculosis therapy

Drug-induced liver injury (DILI) is a known adverse effect of anti-tuberculosis therapy and ART and is a common problem in HIV/TB co-infected patients. First-line TB medicines associated with DILI include isoniazid (INH), rifampicin (RIF) and pyrazinamide (PZA). Anti-tuberculosis therapy commonly causes transient, mild, asymptomatic elevations in serum aminotransferase levels that may not necessarily require discontinuation of therapy.

If hepatitis develops, as defined above, stop all antiretrovirals, cotrimoxazole and all potentially hepatotoxic TB medicines (i.e. INH, RIF and PZA).

TB immune reconstitution inflammatory syndrome (TB-IRIS) should be considered in the differential diagnosis (see Section 10.1.2: Immune reconstitution inflammatory syndrome (IRIS)). This condition presents shortly after ART initiation in patients with TB. The GGT and ALP are elevated to a greater degree than the transaminases. Mild jaundice with a conjugated hyperbilirubinaemia and tender hepatosplenomegaly may be present.

Investigations:
» Request an ALT.
» Request viral hepatitis screen, full liver function tests and INR in patients if ALT >5 x ULN and/or jaundice and/or symptoms of hepatitis are present.
» Perform a liver ultrasound if GGT or ALP are significantly elevated or if conjugated bilirubin is elevated, to exclude extrahepatic biliary obstruction.
» Reassess the grounds for TB diagnosis.
» Check if patient is on intensive or continuation phase of TB treatment.

Management:

» Stop TB therapy, initiate background TB therapy and continue throughout rechallenge:
  - Linezolid, oral 600 mg daily. R (Amikacin, IV/IM, 15 mg/kg daily A is an alternative if Hb <8g/dL, but only for short term use).
  - Levofloxacin, oral, 750–1000 mg daily W or Moxifloxacin, oral, 400 mg daily. W
  - Ethambutol, oral, 800–1200 mg daily.
» Stop cotrimoxazole prophylaxis.
» Stop ART as described above.
» Repeat ALT and bilirubin in 2 days (inpatient) or 7 days (outpatient).
» When ALT is <100 IU/L and total bilirubin is less than twice the upper limit of normal, start TB medicine rechallenge as follows:

Day 1:	• Rifampicin, oral 600 mg daily. W ○ If <60 kg: rifampicin, oral 450 mg daily.
Day 3:	» Check ALT.
Day 4–6:	**ADD** • Isoniazid, oral 300 mg daily.
Day 7:	» Check ALT.
Day 8:	» Stop moxifloxacin/levofloxacin and linezolid (continue ethambutol). Consider pyrazinamide rechallenge only in cases of TB meningitis or intolerance/resistance to other medicines. • Pyrazinamide, oral 25 mg/kg daily.
Day 10:	» Check ALT. » Thereafter, monitor ALT twice weekly for the first 3 weeks, then every two weeks for a month, then monthly until 3 months. • Restart ART 2 weeks after completing rechallenge of TB therapy. ○ Monitor ALT every 2 weeks for 2 months after ART rechallenge.

Table 10.8: Management of drug-induced liver injury (DILI) *LoE:IVb^{xxx}*

» If drug rechallenge is unsuccessful, then manage as per algorithm in Figure 10.2.

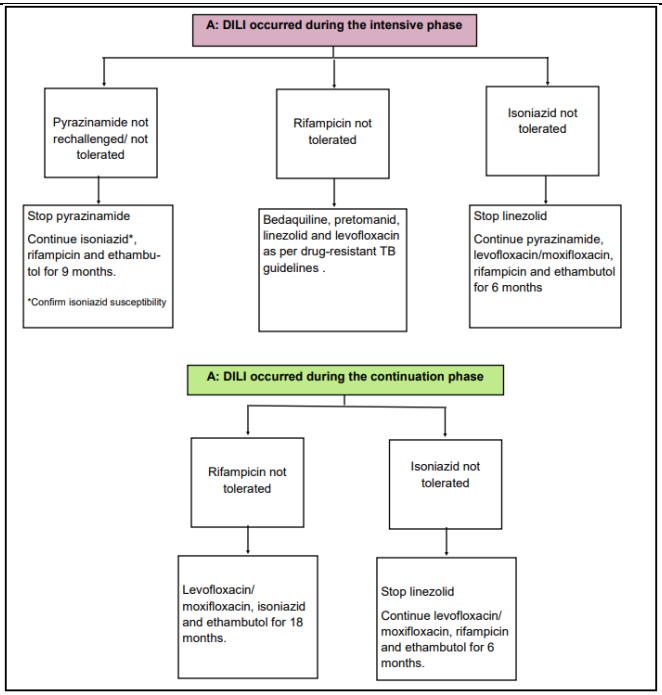


Figure 10.2: Management of TB if drug re-challenge unsuccessful

10.1.2 IMMUNE RECONSTITUTION INFLAMMATORY SYNDROME (IRIS)

D89.3 + (Y41.5 + B24)

DESCRIPTION

IRIS occurs when improving immune function unmasks a previously occult opportunistic disease ("unmasking IRIS") or causes paradoxical deterioration of an existing opportunistic disease ("paradoxical IRIS"). IRIS is more common in patients with advanced HIV disease, particularly those with a CD4 count <100 cells/mm^3. IRIS nearly always presents during the first 3 months of ART, with the median time of onset being about two weeks. The diagnosis of paradoxical IRIS is often difficult as new opportunistic diseases, or drug resistance of the organism causing the opportunistic infection, need to be excluded.

TB is the commonest opportunistic disease involved in IRIS reactions in South Africa. Paradoxical TB IRIS presents as recurrence or worsening of TB symptoms/signs, or new manifestations. The commonest presentation is with

enlarging lymph nodes, often with extensive caseous necrosis. Lung infiltrates or effusions may worsen or develop. It is important to exclude multi-drug resistance in all patients with suspected paradoxical TB IRIS.

Other common IRIS manifestations include:
» Inflammatory reactions to skin diseases, especially acne and Kaposi's sarcoma.
» Worsening cryptococcal meningitis.
» Flares of hepatitis B or C.

GENERAL MEASURES

Counselling is important to ensure that the patient understands that IRIS does not mean failure of ART.
Management of IRIS is mainly symptomatic, e.g. aspiration of TB lymph nodes or effusions.
Continue ART and therapy for the opportunistic infection.

MEDICINE TREATMENT

For pain and fever:

- Paracetamol, oral, 500 mg to 1 g, 4 to 6 hourly as required (to a maximum of 4 g in 24 hours).
  - Maximum dose: 15 mg/kg/dose.

OR

- NSAID, e.g.:
- Ibuprofen, oral, 400 mg 8 hourly with meals.

Treatment for severe IRIS manifestations (e.g. compression of major structures by enlarging lymph nodes, expanding CNS tuberculomata, worsening meningitis):

- Corticosteroids (intermediate-acting) e.g.:
- Prednisone, oral, 1.5 mg/kg daily for 2 weeks.
  - Then 0.75 mg/kg daily for 2 weeks.

Prophylaxis for paradoxical TB IRIS in high-risk patients (CD4 ≤100 cells/mm^3) who have had antituberculosis treatment for <30 days before initiating ART:

- Corticosteroids (intermediate-acting) e.g.:
- Prednisone, oral, 40 mg daily for 2 weeks.
  - Then 20 mg daily for 2 weeks. *LoE:IIa*[xxxi]

Note: Do not use steroids in patients with Kaposi sarcoma.

10.2 OPPORTUNISTIC DISEASES

10.2.1 TUBERCULOSIS PREVENTIVE THERAPY (TPT)

Z29.2 + (B24)

DESCRIPTION

Patients with HIV infection at any CD4 count are more susceptible to TB infection than HIV-negative patients. TPT is an effective intervention for reducing the incidence of TB in HIV-infected patients

Eligibility

All HIV-infected patients, irrespective of CD4 count, tuberculin skin test status, and ART status.

Exclusions

- » Suspected or confirmed TB
- » Liver Disease
- » Previous MDR- or XDR-TB
- » Painful peripheral neuropathy
- » Alcohol use disorder

Note:

- » Exclude TB prior to initiating TPT by screening for the following:
  - Cough (any duration)
  - Fever
  - Weight loss
  - Night sweats
- » Do not initiate TPT in patients if any of the above is present. These patients require further investigation for active TB.

Ideally start TPT together with ARVs: *LoE:IIb*[xxxii]

- TPT, e.g.:
- Isoniazid, oral, 300 mg daily for 12 months.
  - Educate patients on the symptoms of hepatotoxicity (nausea, vomiting, yellow eyes, brown urine, and pain in right upper quadrant) associated with TPT.

Note: For adults and adolescents initiating a DTG-containing ART regimen, isoniazid daily for 12 months is the preferred regimen. For patients who are already virally suppressed on a DTG-based regimen, a weekly combination of isoniazid (900mg if weight >30 kg) plus rifapentine (900mg if weight >30 kg) for three months may be preferred. Do not use rifapentine-containing TPT in patients on protease inhibitor-based ART, or in women on hormonal contraceptives. *[See the therapeutic interchange database for details regarding the rifapentine-containing TPT regimen.]*

LoE:IIb[xxxiii]

ADD

- Pyridoxine, oral, 25 mg once daily for the full duration of the TPT regimen.
  - Instruct patient to present early if any of these symptoms arise.
  - Patients should be followed up monthly for the first 3 months.

NOTE: **For pregnant women:**
- Defer TPT until after delivery.
- Ensure that routine screening against TB is conducted at each antenatal visit.

LoE:IIb[xxxiv]

10.2.2 OPPORTUNISTIC INFECTION PROPHYLAXIS, WITH COTRIMOXAZOLE

Z29.2 + (B24)

DESCRIPTION

Primary prophylaxis reduces the probability of developing many infections, e.g.:
- » Pneumocystis pneumonia
- » toxoplasmosis
- » bacterial pneumonia
- » bacteraemia
- » cystoisosporiasis

LoE:IIa[xxxv]

Indications for primary prophylaxis:
- » WHO Clinical stage III or IV.
- » CD4 count <200 cells/mm^3.

MEDICINE TREATMENT

Prophylaxis

- Cotrimoxazole, oral, 160/800 mg daily. A

LoE:IIa[xxxvi]

Note:

Discontinue prophylaxis once the CD4 >200 cells/mm^3 (as measured at the routine CD4 count done at 1 year on ART). If the CD4 count was >200 cells/mm^3 when cotrimoxazole was commenced (e.g. patients with TB), continue for 6 months.

LoE:IIIb[xxxvii]

10.2.3 CANDIDIASIS OF OESOPHAGUS/TRACHEA/BRONCHI

B20.4

DESCRIPTION

Mucosal candidiasis involving the oesophagus/trachea/bronchi is AIDS-defining (WHO clinical stage 4). Oesophagitis is by far the commonest manifestation.

Clinical features: symptoms of pain or difficulty on swallowing. Oral thrush is present in most patients.

GENERAL MEASURES

Maintain adequate hydration.

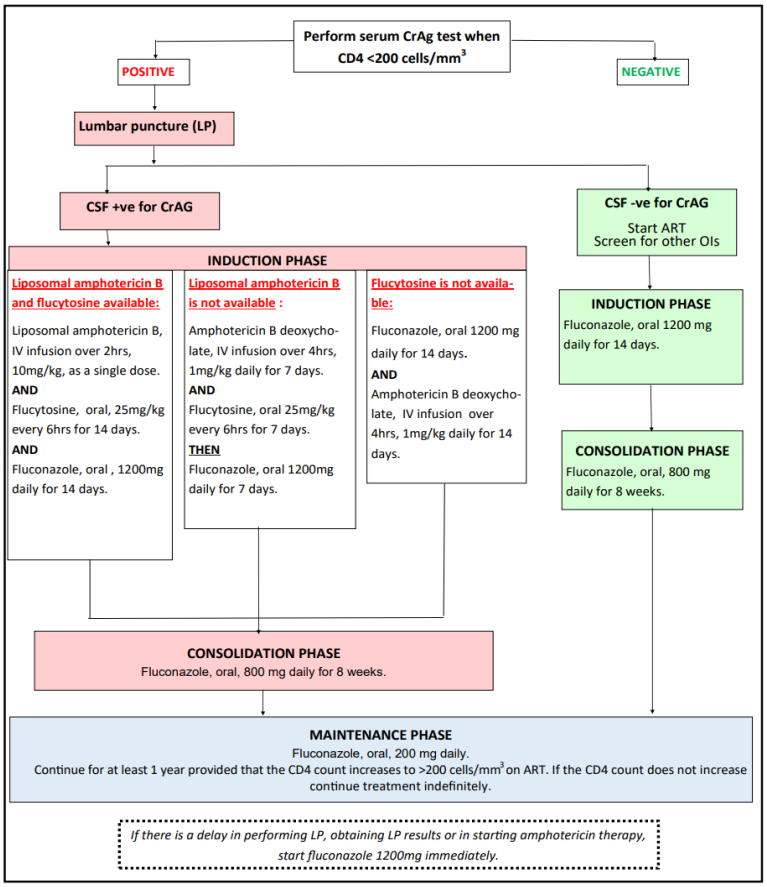
MEDICINE TREATMENT

- Fluconazole, IV/oral, 200 mg daily for 14 days.

- The usual route is oral but give IV if patient unable to swallow or is vomiting.
- An early relapse should be treated with a 4-week course of fluconazole, using a similar dose as above.
- If no response to fluconazole, collect sample to confirm diagnosis of candidiasis (perform fungal MC&S).

Note: Primary or secondary fluconazole prophylaxis for mucosal candidiasis is not recommended.

10.2.4 CRYPTOCOCCOSIS



Adapted from: Govender NP, Meintjes G, Mangena et al. Southern African HIV Clinicians Society guideline for the prevention, diagnosis and management of cryptococcal disease among HIV-infected persons: 2019 update. S Afr J HIV Med 2019;20(1):a1030. https://doi.org/10.4102/sajhivmed.v20i1.1030

Figure 10.3: Algorithm for the prevention, diagnosis and management of cryptococcal disease among HIV-infected persons

10.2.4.1 CRYPTOCOCCOSIS, CSF CRAG NEGATIVE

(B45.0-3/B45.7-9) + B20.5

DESCRIPTION

All ART-naïve patients with CD4 <200 cells/mm^3 should have cryptococcal antigen (CrAg) test done on serum, plasma or whole blood (unless they had a diagnosis of cryptococcal infection). This is performed as a reflex test on the patient's CD4 sample if it is <100 cells/mm^3. If the CD4 count is between 100 and 199, a separate sample should be sent for CrAg testing. If the CrAg test is positive, all patients should have a lumbar puncture, regardless of whether symptoms of meningitis are present, since asymptomatic cryptococcal meningitis may be present. Confirm cryptococcal meningitis by testing for CSF CrAg.

LoE:IIa[xxxviii]

MEDICINE TREATMENT

<u>If cryptococcal meningitis is excluded by negative CSF CrAg:</u>
Commence ART immediately - see Section 10.1: Antiretroviral therapy.

LoE:IIIa[xxxix]

Induction phase

- Fluconazole, oral 1200 mg daily for 14 days.

Consolidation phase

Follow with:

- Fluconazole, oral, 800 mg daily for 8 weeks.

Maintenance phase

LoE:IIIb[xl]

- Fluconazole, oral, 200 mg daily.
  - Continue for at least 1 year provided that the CD4 count increases to >200 cells/mm^3 on ART. If the CD4 count does not increase, continue treatment indefinitely.

CAUTION

» Fluconazole is potentially teratogenic when used during the 1st trimester, but pregnant women should be counselled that the benefits of fluconazole likely outweigh the risks in the management of cryptococcosis.

» All pregnant women <20 weeks gestation exposed to fluconazole should have an ultrasound scan to detect congenital abnormalities. *LoE:IIIb*[xli]

» Although fluconazole is excreted into breast milk at concentrations similar to maternal plasma concentrations, the dose that the infant is exposed to with doses <400 mg is similar to the dose used in systemic treatment in infants. The benefits will likely outweigh the risks, even with higher doses, though this can be discussed with a specialist.

LoE:IVb[xlii]

10.2.4.2 CRYPTOCOCCAL MENINGITIS

B20.5 + (B45.1 + G02.1*)

DESCRIPTION

Cryptococcal meningitis is the commonest manifestation of disseminated cryptococcosis in patients with advanced HIV. Severe headache is common due to raised intracranial pressure.

Diagnosis

Confirmed on lumbar puncture.

GENERAL MEASURES

Therapeutic lumbar puncture is indicated to lower pressure in symptomatic patients and should be done with pressure monitoring. Remove sufficient CSF (maximum 30 mL) to lower pressure to 50% of the opening pressure but not less than 20 cm H_2O.

Continue daily therapeutic lumbar puncture until there is clinical improvement.

MEDICINE TREATMENT

Induction phase

<u>If liposomal amphotericin B and flucytosine are available:</u> *LoE:IVb[xliii]*

- Liposomal amphotericin B, slow IV infusion over 2 hours, 10 mg/kg in dextrose 5%, single dose.

AND

- Flucytosine, oral 25 mg/kg 6 hourly for 14 days (see flucytosine weight-based dosing table below).
  - Flucytosine requires dose adjustment in renal failure (see Appendix II for preventing, monitoring and management of toxicity).

AND *LoE:IIa[xliv]*

- Fluconazole, oral 1200 mg daily for 14 days.
  - Fluconazole requires dose adjustment in renal failure.

<u>If liposomal amphotericin B is not available:</u>

- Amphotericin B deoxycholate, slow IV infusion, 1 mg/kg daily in dextrose 5% over 4 hours for 7 days.
  - Ensure adequate hydration to minimise nephrotoxicity (see Appendix II for preventing, monitoring and management of toxicity).

AND

- Flucytosine, oral 25 mg/kg 6 hourly for 7 days (see flucytosine weight-based dosing table below).
  - Flucytosine requires dose adjustment in renal failure (see Appendix II for preventing, monitoring and management of toxicity).

THEN (i.e. days 8-14 of induction phase):

- Fluconazole, oral 1200 mg daily for 7 days. LoE:IVb[xlv]

<u>If flucytosine is not available:</u>

- Fluconazole, oral 1200 mg daily for 14 days.

AND LoE:IIa[xlvi]

- Amphotericin B deoxycholate, slow IV infusion, 1 mg/kg daily in dextrose 5% over 4 hours for 14 days.
  - Ensure adequate hydration to minimise nephrotoxicity. (see Appendix II for preventing, monitoring and management of toxicity).

Consolidation phase

Follow with: LoE:IIIa[xlvii]

- Fluconazole, oral, 800 mg daily for 8 weeks.

Maintenance phase LoE:Ia[xlviii]

- Fluconazole, oral, 200 mg daily.
  - Continue for at least 1 year provided that the CD4 count increases to >200 cells/mm^3 on ART. If the CD4 count does not increase, continue treatment indefinitely.

- Commence ART 4–6 weeks after starting antifungal therapy. See Section 10.1: Antiretroviral therapy.

LoE:IIIa[xlix]

Note: Adjunctive corticosteroids have been shown to be detrimental. LoE:Ia[l]

Flucytosine weight-based dosing:

Weight	Dose and frequency
30-39 kg	750 mg 6 hourly
40-49 kg	1000 mg 6 hourly
50-59 kg	1250 mg 6 hourly
60-69 kg	1500 mg 6 hourly
70-79 kg	1750 mg 6 hourly

Table 10.9: Flucytosine weight-based dosing

REFERRAL

» Focal neurological signs – CT scan required to exclude other pathology e.g. toxoplasmosis.

» Persistent raised intracranial pressure despite daily therapeutic lumbar puncture.

10.2.5 CRYPTOSPORIDIOSIS DIARRHOEA

A07.2 + (B20.8)

DESCRIPTION

Chronic diarrhoea due to *Cryptosporidium parvum*. Disease lasting >4 weeks is AIDS-defining (WHO clinical stage 4).

GENERAL MEASURES

Rehydration with oral rehydration solution (ORS).

MEDICINE TREATMENT

There is no specific antimicrobial therapy for cryptosporidiosis. As with other opportunistic diseases, it responds well to ART.

Antimotility agents are partially effective, e.g.:

- Loperamide, oral, 4 mg initially, followed by 2 mg as required up to four times daily.

10.2.6 CYTOMEGALOVIRUS (CMV)

B20.2

DESCRIPTION

CMV disease outside the reticulo-endothelial system is an AIDS-defining illness (WHO clinical stage 4).
CMV disease is seen in patients with CD4 counts <100 cells/mm^3.
The commonest manifestations are:

» retinitis,
» GIT ulceration,
» pneumonitis, and
» polyradiculitis.

GIT and other organ involvement must be diagnosed on biopsy.
CNS disease must be diagnosed by PCR of CSF.
The diagnosis of CMV retinitis should be confirmed by an ophthalmologist.
Note: CMV serology (IgM and IgG), antigenaemia (pp65), or PCR on blood are not helpful in the diagnosis of CMV disease in HIV-infected adults.

MEDICINE TREATMENT

Valganciclovir is the treatment of choice, but this agent is toxic and expensive and should only be used by a specialist familiar with its use.
To prevent recurrent disease, commence patients on ART as soon as possible after initiating valganciclovir (see Section 10.1: Antiretroviral therapy).
Maintenance therapy is only applicable to CNS disease and retinitis.
Monitor FBC regularly during therapy. Avoid other medicines associated with bone marrow suppression, particularly zidovudine.

Biopsy-proven GIT disease or pneumonitis

- Valganciclovir, oral, 900 mg 12 hourly for the first 3 weeks. Specialist initiated.

OR

If unable to tolerate oral medication:

- Ganciclovir, IV, 5 mg/kg 12 hourly for 14 days. Specialist initiated.

CNS disease

Initial treatment:

- Valganciclovir, oral, 900 mg 12 hourly for the first 3 weeks. Specialist initiated.

OR

If unable to tolerate oral medication:

- Ganciclovir, IV, 5 mg/kg 12 hourly for 14 days. Specialist initiated.

Maintenance treatment:

Only patients with a good clinical response should be considered for maintenance.

Valganciclovir, oral, 900 mg daily until CD4 count rises to >100 cells/mm^3 on ART, if available. Specialist initiated.

Note: Maintenance treatment is not indicated unless there has been a relapse.

REFERRAL/CONSULTATION

Specialist or tertiary

All patients.

10.2.7 CYSTOISOSPORIASIS

A07.3 + (B20.8)

DESCRIPTION

Diarrhoea due to *Cystoisospora belli*. Disease lasting >4 weeks is AIDS-defining (WHO clinical stage 4).

GENERAL MEASURES

Rehydration with oral rehydration solution (ORS).

MEDICINE TREATMENT

- Cotrimoxazole 160/800 mg, oral, 2 tablets 12 hourly for 10 days. A

OR

If allergic to cotrimoxazole:

- Ciprofloxacin, oral, 500 mg 12 hourly for 10 days. W

Secondary prophylaxis:
Continue for at least 6 months and until CD4 count increases to >200 cells/mm^3 on ART.

- Cotrimoxazole 160/800 mg, oral daily.

10.2.8 MYCOBACTERIOSIS – DISSEMINATED NON-TUBERCULOUS

B20.0

DESCRIPTION

Disseminated infection due to non-tuberculous mycobacteria, usually *Mycobacterium avium* complex.
Diagnosis must be by culture from sterile sources, e.g. blood, tissue or bone marrow. Note that culture from a single sputum specimen is not adequate to make the diagnosis as this often reflects colonisation rather than disease.
Non-tuberculous mycobacteria can cause limited pulmonary disease, which is diagnosed if the sputum culture is positive repeatedly and there is a worsening pulmonary infiltrate.
Disseminated disease is AIDS-defining (WHO clinical stage 4).

MEDICINE TREATMENT

- Azithromycin, oral, 500 mg daily. W

AND *LoE:IIIa*[ii]

- Ethambutol, oral, 15–20 mg/kg daily.

Treatment can be stopped when treatment has been continued for at least 12 months **AND** the CD4 count has increased to >100 cells/mm^3 on ART.

10.2.9 PNEUMOCYSTIS PNEUMONIA

B20.6

DESCRIPTION

Interstitial pneumonitis due to *Pneumocystis jirovecii* (formerly *carinii*). AIDS-defining illness (WHO clinical stage 4).

MEDICINE TREATMENT

All patients:

- Cotrimoxazole 80/400 mg, oral, 6 hourly for 21 days. A
  - <60 kg three tablets
  - ≥60 kg four tablets

Monitor FBC and potassium when on high dose therapy.

OR

If vomiting:

- Cotrimoxazole, IV, 6 hourly for 21 days. A
  - <60 kg 240/1200 mg

- ≥60 kg 320/1600 mg

For hypoxic patients (PaO_2 <70 mmHg [<9.33 kPa], A-a gradient >35, or sats <92%):

- Oxygen by face mask or CPAP as necessary.

AND

- Corticosteroids (intermediate-acting) e.g.:
- Prednisone, oral, 80 mg daily for 5 days, then taper over 14 days. (Refer to Appendix II for an example of a dose reduction regimen.)

Cotrimoxazole intolerance and desensitisation

Attempt desensitisation in patients with a history of cotrimoxazole intolerance, unless hypersensitivity reaction was life-threatening, e.g. Stevens-Johnson syndrome (see Section 4.6: Erythema Multiforme, Stevens Johnson Syndrome, Toxic Epidermal Necrolysis). Unless rash is severe or associated with systemic symptoms, continue treatment with careful observation for deterioration.

Desensitisation should be attempted using cotrimoxazole suspension 240 mg/5 ml. Dilute the suspension appropriately and consult with your pharmacist if necessary. DO NOT administer antihistamines or steroids.

Time (hours)	Cotrimoxazole dose (mL of 240mg/5mL suspension
0	0.0005
1	0.005
2	0.05
3	0.5
4	5
5	Two single strength tablets (each tablet = 80/400 mg) followed by full dose

Table 10.10: Desensitisation of cotrimoxazole

Alternatively, in case of intolerance and unsuccessful desensitisation:

- Clindamycin, oral, 600 mg 8 hourly for 21 days.

AND

- Primaquine, oral, 15 mg daily for 21 days.
  - Exclude G6PD deficiency before initiating therapy.
  - Primaquine is only available via the Section 21 application process.

If primaquine is not available, consider:

- Clindamycin, oral, 600 mg 8 hourly for 21 days. A

AND

- Dapsone, oral, 100 mg daily for 21 days.

Secondary prophylaxis

Continue for at least 6 months and until CD4 count increases to >200 cells/mm^3 on ART.

- Cotrimoxazole 160/800 mg, oral daily. A

Alternatively, in case of intolerance to cotrimoxazole:
- Dapsone, oral, 100 mg daily.

REFERRAL/CONSULTATION
Specialist or tertiary
Intolerance to all alternative regimens.

10.2.10 CEREBRAL TOXOPLASMOSIS
B58 + (B20.8)

DESCRIPTION
Intracranial space-occupying lesions, with ring contrast enhancement on imaging, due to *Toxoplasma gondii*. AIDS-defining illness (WHO clinical stage 4).

The diagnosis of toxoplasmosis is very unlikely if either the serum toxoplasma IgG is negative or the CD4 count is >200 cells/mm^3.

Diagnosis is confirmed by a clinical response to therapy, which occurs in 7–14 days. CT scan improvement usually occurs within 14–21 days. Interpreting the response to therapy may be difficult if steroids have been given concomitantly. Steroid therapy should only be given for life-threatening peri-lesional oedema.

MEDICINE TREATMENT
- Cotrimoxazole 160/800 mg, oral, 2 tablets 12 hourly for 28 days, followed by 1 tablet 12 hourly for 3 months. A

Secondary prophylaxis
Continue for at least 6 months and until CD4 count increases to > 200 cells/mm^3 on ART.
- Cotrimoxazole 160/800 mg, oral, 2 tablets daily. A

See guidance on cotrimoxazole desensitisation in Section 10.2.9: Pneumocystis pneumonia.

REFERRAL/CONSULTATION
Specialist or tertiary
Intolerance to cotrimoxazole.
Note: Attempt desensitisation first (see Section 10.2.9: Pneumocystis pneumonia).

10.3 HIV AND KIDNEY DISEASE

N28.9 + (B23.8)

DESCRIPTION

A number of kidney disorders are associated with HIV infection.
Acute kidney injury due to sepsis, dehydration or nephrotoxicity from medicines occurs commonly.

The commonest chronic kidney disorder is HIV-associated nephropathy (HIVAN).
Typical features of HIVAN are:

» Heavy proteinuria.
» Rapidly progressive chronic kidney disease with preserved kidney size on imaging.

Early detection of kidney disease is important in order to implement interventions that may slow kidney disease progression, and for adjusting the dose of relevant medicines.
Risk factors for HIV renal disease:

» CD4 count <200 cells/mm^3.
» Use of nephrotoxic medications.
» Comorbidity such as diabetes mellitus, hypertension, or hepatitis C virus co-infection.
» ART may slow progression of HIVAN.

Screening for renal disease in HIV

» Tests should include:
  – Urine dipstick for haematuria and proteinuria (request urine protein:creatinine ratio if proteinuria is detected; discuss with a specialist if >0.15 g/mmol).
  – Serum creatinine and eGFR.

Dose adjustment of ART in renal impairment: Refer to Table 10.2: Dosing and important adverse effects associated with ART in Section 10.1: Antiretroviral therapy.

10.4 KAPOSI SARCOMA (KS)

B21.0

DESCRIPTION

Kaposi Sarcoma (KS) is a malignancy of lymphatic endothelial origin associated with Human Herpes Virus-8, also known as KS Herpes Virus, infection.
KS may involve the skin, oral cavity, lymph nodes or viscera (especially lung and GIT).
Most patients have multiple lesions.
Lymphoedema is a common complication.
10–20% of cases of visceral KS will have no oral or skin involvement.
KS is an AIDS-defining illness (WHO clinical stage 4).

Although most cases are diagnosed on the typical macroscopic appearance of skin and oral lesions, biopsy confirmation is necessary for atypical lesions and consideration for chemotherapy. One important differential diagnosis is bacillary angiomatosis, which develops more rapidly.

MEDICINE TREATMENT

All patients with KS should be commenced on ART (see Section 10.1: Antiretroviral therapy) and cotrimoxazole prophylaxis (see Section 10.2.2: Opportunistic infection prophylaxis, with cotrimoxazole) regardless of CD4 count. Many patients with limited mucocutaneous KS will have complete resolution or substantial regression on ART alone.

REFERRAL

Prior to referral, all patients must be started on ART.

» Radiotherapy/intralesional chemotherapy for symptomatic local lesions.
» Systemic chemotherapy is indicated in patients with poor prognostic factors:
  - more than 25 skin lesions,
  - rapidly progressive disease,
  - visceral involvement,
  - extensive oedema, or
  - "B" symptoms, i.e. fever, night sweats, significant constitutional symptoms.
» Failure of KS to respond to ART.

10.5 POST-EXPOSURE PROPHYLAXIS

National HIV Health Care Worker Hotline: 0800 212 506 or 021 406 6782.

10.5.1 POST-EXPOSURE PROPHYLAXIS, OCCUPATIONAL

S61.0 + (W46.22 + Z20.6 + Z29.8)

DESCRIPTION

Antiretroviral therapy may prevent the risk of acquiring HIV following a significant occupational exposure.

It is essential to document occupational exposures adequately for possible subsequent compensation.

Other blood borne infections (hepatitis B and C) should also be tested for in the source patient and appropriate prophylaxis instituted in the case of hepatitis B.

Assessing the risk of occupational exposures

The risk of acquiring HIV following occupational exposure is determined by the nature of the exposure and the infectiousness of the source patient. High-risk exposures involve exposure to a larger quantity of viruses from the source patient, either due to exposure to larger quantity of blood or because the amount of virus in the blood is high.

Any one of the following is associated with an increased risk of HIV transmission:
» deep percutaneous sharps injuries,
» percutaneous exposure involving a hollow needle that was used in a vein or artery,
» visible blood on the sharp instrument involved in a percutaneous injury,
» the source patient has terminal AIDS or is known to have a high viral load, i.e. >100 000 copies/mL.

In instances when the risk of infection is extremely low or non-existent, post-exposure prophylaxis (PEP) is not indicated, as the risks of PEP will far outweigh the benefits. PEP is **NOT** indicated when:
» The material the healthcare worker was exposed to is not infectious for HIV in the occupational setting, e.g. vomitus, urine, faeces or saliva, unless these are visibly blood stained.
» The exposure was on intact skin.
» The source patient is HIV negative, unless there are clinical features to suggest seroconversion illness, in which case PEP should be commenced until further tests are done – consult with a virologist or infectious diseases specialist.
» The healthcare worker is HIV infected, as this person should be assessed for ART initiation.

PEP REGIMENS
PEP should be commenced as soon as possible after the injury. Do not delay initiating PEP while awaiting confirmatory test results on the source patient and health care worker. PEP should be considered up to 72 hours after exposure and, in exceptional circumstances involving high-risk exposures, PEP may be considered up to 7 days after exposure.

When PEP is indicated (administered preferably as a fixed-dose combination):
- Tenofovir disoproxil fumarate (TDF), oral, 300 mg daily for 4 weeks (provided baseline eGFR is >50 mL/minute. Do not delay initiation of PEP while awaiting baseline eGFR. Re-assess TDF eligibility once results become available).

AND
- Lamivudine, oral, 300 mg daily for 4 weeks

AND
Dolutegravir, oral 50 mg daily for 4 weeks. *LoE:IIIa*[lii]

If DTG is not tolerated:
- Tenofovir disoproxil fumarate, oral, 300 mg daily for 4 weeks (provided baseline eGFR is >50 mL/minute).

AND
- Emtricitabine, oral, 200 mg daily for 4 weeks.

AND *LoE:IIIb*[liii]

- Atazanavir/ritonavir 300/100 mg, 1 tablet, oral daily for 4 weeks.

OR

- Lopinavir/ritonavir 200/50 mg, oral, 2 tablets 12 hourly for 4 weeks.

If TDF is contraindicated or if source patient is known to be failing a TDF-based regimen, replace TDF and emtricitabine with:

- Zidovudine, oral, 300 mg 12 hourly for 4 weeks.

AND

- Lamivudine, oral, 150 mg 12 hourly for 4 weeks.

AND

- Continue third applicable drug (DTG or boosted PI – see above).

PEP is generally not well tolerated. Adverse effects occur in about half of cases and therapy is discontinued in about a third. Efavirenz is not recommended as it is very poorly tolerated in PEP.

Zidovudine often causes nausea and headache and so should only be given if TDF is contraindicated.

Lopinavir/ritonavir often causes diarrhoea. If lopinavir/ritonavir is not tolerated switch to atazanavir/ritonavir. Atazanavir/ritonavir often causes unconjugated jaundice, which is benign but may not be tolerated, in which case switch to lopinavir/ritonavir. If both these protease-inhibitors are not well tolerated, consult a specialist.

Recommendations for post exposure prophylaxis (PEP) after occupational exposure to infectious material (includes blood, CSF, semen, vaginal secretions and synovial/pleural/ pericardial/ peritoneal/amniotic fluid) from HIV seropositive patients are given in the table, below.

Exposure	**HIV Status of source patient**	
	Negative	**Unknown or Positive**
Intact skin	no PEP	no PEP
Mucosal splash **or** **non-intact skin** **or** **percutaneous injury**	no PEP	PEP: • TDF+3TC+DTG **OR** • Other 3-drug regimen

Table 10.11: PEP for healthcare worker following occupational HIV exposure

When the source patient is known to be failing ART, modify the PEP regimen:

» If the patient is on zidovudine, use TDF

» If the patient is on TDF, use zidovudine.

	Source patient			
	Vaccination status	**HBsAg positive**	**HbsAg negative**	**HBsAg unknown**
Vaccination status and antibody response status of HCW	Unvaccinated or vaccination incomplete	• HBIG, IM, 500 units* • Hep B vaccine (3 doses at monthly intervals)	• Initiate Hep B vaccination (month 0, 1 and 6)	• HBIG, IM, 500 units* • Hep B vaccine (3 doses at monthly intervals)
	Vaccinated **AND** known to have HBsAb ≥10 units/mL#	No treatment	No treatment	No treatment
	Vaccinated **AND** HBsAb <10 units/mL or level unknown	• HBIG, IM, 500 units * • If HBIG <10 units/mL, repeat HBIG at 1 month • Repeat Hep B vaccine (3 doses at monthly intervals)	No treatment	• HBIG, IM, 500 units* • If HBIG <10 units/mL, repeat HBIG at 1 month • Repeat Hep B vaccine (3 doses at monthly intervals)

Table 10.12: PEP for healthcare workers following hepatitis B exposure

LoE:IVb[iv]

* HBIG and first dose of vaccine to be given simultaneously, but at different sites.

If the delay in obtaining HBsAb results is more than 7 days initiate treatment as for vaccinated AND HBsAb < 10 units/mL.

After vaccination ensure the health care worker has a HBsAb > 10 units/mL 1 – 2 months after the last vaccine dose.

LoE:IVb[iv]

Test	**Source patient**	**Exposed health care worker**			
	Baseline	**Baseline**	**2 weeks**	**6 weeks**	**4 months**
HIV	Rapid test **PLUS** ELISA	Rapid test **PLUS** ELISA		ELISA	ELISA
Hepatitis B	Surface antigen	Surface antibody**			Surface antigen and surface antibody**
Hepatitis C	HCV antibody	HCV antibody*		HCV PCR*	
Syphilis	RPR/ TP antibody	RPR/TP antibody*			RPR/TP antibody*
Creatinine		If TDF part of PEP	If TDF part of PEP		
FBC		If AZT part of PEP	If AZT part of PEP		

Table 10.13: Investigations and monitoring in occupational exposures

*Only if source patient was positive (in the case of syphilis, source patient must be RPR positive)

**Only if source patient was positive AND health care worker unvaccinated or HBsAb <10 units/mL

10.5.2 NON-OCCUPATIONAL POST EXPOSURE PROPHYLAXIS, SEXUAL ASSAULT

Z29.8

PEP should be offered to rape survivors who present within 72 hours (management is the same as for occupational HIV exposure. See Section 10.5.1: Post-exposure prophylaxis, occupational).
A patient presenting ≥72 hours since the alleged incident should not be given PEP but should be counselled about the possible risk of transmission, with HIV testing provided at the time of presentation and 4 months later. Rape survivors who test HIV seropositive should be initiated on ART– see Section 10.1: Antiretroviral therapy.
Other important aspects of care for the rape survivor should not be forgotten, i.e. contraception, treatment for sexually transmitted infections, counselling and forensic specimens.

Emergency contraception after pregnancy is excluded
Do a pregnancy test in all women and female adolescents. Children must be tested and given emergency contraception from Breast Tanner Stage III. If unsure of staging, give emergency contraception when you detect any breast development (DO NOT REGARD MENARCHE AS AN INDICATION).

- Copper IUCD, e.g.:
- Cu T380A, inserted as soon as possible after unprotected intercourse and not later than 5 days.

LoE:IIIb[lvi]

OR

- Levonorgestrel 1.5 mg, oral, as a single dose as soon as possible after unprotected intercourse, and not later than 5 days.
  - If the woman vomits within 2 hours, repeat the dose.
  - Advise women that their period should be on time; very rarely it is delayed but it should not be more than 7 days late. If this occurs, they should come back for a pregnancy test.

LoE:Ia[lvii]

CAUTION

Emergency contraceptive tablets must be taken as soon as possible, preferably within 72 hours of unprotected intercourse, and not later than 5 days.
Enzyme inducers (including efavirenz and carbamazepine) cause a significant reduction in levonorgestrel concentrations.
Women on these medicines should preferably have copper IUCD inserted or alternatively double the dose of levonorgestrel.
Women >80 kg or BMI ≥30 should also preferably have copper IUCD inserted or alternatively double the dose of levonorgestrel.

LoE:IIIb[lviii]

An anti-emetic:

LoE:IVb[lix]

- Metoclopramide oral, 10 mg 8 hourly as needed.

STI prophylaxis

- Ceftriaxone, IM, 250 mg as a single dose. W
  - For ceftriaxone IM injection: Dissolve ceftriaxone 250 mg in 0.9 mL lidocaine 1% without epinephrine (adrenaline).

AND

- Azithromycin, oral, 1 g as a single dose. W

LoE:IIIb[lx]

AND

- Metronidazole, oral, 2 g immediately as a single dose. A

HIV PrEP

If patient is at ongoing high risk of HIV acquisition, commence PrEP after PEP has been completed.

Perform HIV test 4 weeks after initiating PrEP. See PHC STGs and EML, Section 11.11: Pre-exposure prophylaxis (PrEP).

10.5.3 NON-OCCUPATIONAL POST EXPOSURE PROPHYLAXIS, INADVERTENT NON-OCCUPATIONAL

Z29.8

Inadvertent (non-occupational) exposure to infectious material from HIV sero-positive persons often requires clinical judgement and includes:

» human bites (requires hepatitis B, but not HIV prophylaxis),
» sharing of needles during recreational drug use,
» consensual sexual exposure, burst condoms,
» contact sports with blood exposure.

LoE:IVb[lxi]

For those who require PEP, management of inadvertent (non-occupational) HIV exposure is the same as for occupational HIV exposure. See Section 10.5.1: Post-exposure prophylaxis, occupational.

References:

[i]South African National Department of Health. 2023 Antiretroviral Therapy Clinical Guidelines for the Management of HIV in Adults, Pregnancy and Breastfeeding, Adolescents, Children, Infants and Neonates. April 2023. Accessible at https://knowledgehub.health.gov.za/system/files/elibdownloads/2023-07/National%20ART%20Clinical%20Guideline%20AR%204.5%2020230713%20Version%204%20WEB.pdf

[ii]Eligibility for ART: INSIGHT START Study Group, Lundgren JD, Babiker AG, Gordin F, Emery S, Grund B, Sharma S, Avihingsanon A, Cooper DA, Fätkenheuer G, Llibre JM, Molina JM, Munderi P, Schechter M, Wood R, Klingman KL, Collins S, Lane HC, Phillips AN, Neaton JD. Initiation of Antiretroviral Therapy in Early Asymptomatic HIV Infection. N Engl J Med. 2015 Aug 27;373(9):795-807. http://www.ncbi.nlm.nih.gov/pubmed/26192873

Eligibility for ART: TEMPRANO ANRS 12136 Study Group. A Trial of Early Antiretrovirals and Isoniazid Preventive Therapy in Africa. N Engl J Med. 2015 Aug 27;373(9):808-22. http://www.ncbi.nlm.nih.gov/pubmed/26193126

Eligibility for ART- Immediate initiation of ART: Rosen S, Maskew M, Fox MP, Nyoni C, Mongwenyana C, Malete G, Sanne I, Bokaba D, Sauls C, Rohr J, Long L. Initiating Antiretroviral Therapy for HIV at a Patient's First Clinic Visit: The RapIT Randomized Controlled Trial. PLoS Med. 2016 May 10;13(5):e1002015. https://www.ncbi.nlm.nih.gov/pubmed/27163694

Eligibility for ART- Immediate initiation of ART: National Department of Health: National Consolidated Guidelines for the Management of HIV in Adults, Adolescents, Children and Infants and Prevention of Mother-to-Child Transmission, June 2020. https://www.knowledgehub.org.za/elibrary/national-consolidated-guidelines-management-hiv-adults-adolescents-children-and-infants

[iii] Immediate initiation of ART, pregnant and breastfeeding women: National Department of Health: Affordable Medicines, EDP-Adult Hospital level. Medicine Review: Dolutegravir in pregnant women and women of child-bearing potential (WOCP), 17 June 2021. https://www.knowledgehub.org.za/content/standard-treatment-guidelines-and-essential-medicines-list

Immediate initiation of ART, pregnant and breastfeeding women: WHO. Consolidated guidelines on HIV prevention, testing, treatment, service delivery and monitoring: recommendations for a public health approach, July 2021. https://www.who.int/publications/i/item/9789240031593

[iv]Timing of ART initiation (pulmonary TB): Uthman OA, Okwundu C, Gbenga K, Volmink J, Dowdy D, Zumla A,Nachega JB. Optimal Timing of Antiretroviral Therapy Initiation for HIV-Infected Adults With Newly Diagnosed Pulmonary Tuberculosis: A Systematic Review and Meta-analysis. Ann Intern Med. 2015 Jul 7;163(1):32-9.http://www.ncbi.nlm.nih.gov/pubmed/26148280

[v]Timing of ART initiation (tuberculous meningitis): Török ME, Yen NT, Chau TT, Mai NT, Phu NH, Mai PP, Dung NT, Chau NV, Bang ND, Tien NA, Minh NH, Hien NQ, Thai PV, Dong DT, Anh do TT, Thoa NT, Hai NN, Lan NN, Lan NT, Quy HT, Dung NH, Hien TT, Chinh NT, Simmons CP, de Jong M, Wolbers M, Farrar JJ. Timing of initiation of antiretroviral therapy in human immunodeficiency virus (HIV)--associated tuberculous meningitis. Clin Infect Dis. 2011 Jun;52(11):1374-83. http://www.ncbi.nlm.nih.gov/pubmed/21596680

[vi] Timing of ART initiation (cryptococcal meningitis): Eshun-Wilson I, Okwen MP, Richardson M, Bicanic T. Early versus delayed antiretroviral treatment in HIV-positive people with cryptococcal meningitis. Cochrane Database Syst Rev. 2018 Jul 24;7(7):CD009012. https://pubmed.ncbi.nlm.nih.gov/30039850/

Timing of ART initiation (cryptococcal meningitis): National Department of Health: National Consolidated Guidelines for the Management of HIV in Adults, Adolescents, Children and Infants and Prevention of Mother-to-Child Transmission, June 2020. https://www.knowledgehub.org.za/elibrary/national-consolidated-guidelines-management-hiv-adults-adolescents-children-and-infants

Timing of ART initiation (cryptococcal meningitis): WHO. Consolidated guidelines on HIV prevention, testing, treatment, service delivery and monitoring: recommendations for a public health approach, July 2021. https://www.who.int/publications/i/item/9789240031593

[vii] Timing of ART initiation (asymptomatic cryptococcosis): WHO. Consolidated guidelines on HIV prevention, testing, treatment, service delivery and monitoring: recommendations for a public health approach, July 2021. https://www.who.int/publications/i/item/9789240031593

Timing of ART initiation (asymptomatic cryptococcosis): Govender NP, Meintjes G, Mangena P, Nel J, Potgieter S, Reddy D, Rabie H, et al. Southern African HIV Clinicians Society guideline for the prevention, diagnosis and management of cryptococcal disease among HIV-infected persons: 2019 update. South Afr J HIV Med. 2019 Nov 8;20(1):1030. https://pubmed.ncbi.nlm.nih.gov/32201629/

[viii]Psychosocial indicators of readiness for ART: WHO. Consolidated guidelines on HIV prevention, testing, treatment, service delivery and monitoring: recommendations for a public health approach, July 2021. https://www.who.int/publications/i/item/9789240031593

[ix]Dolutegravir, oral (first-line ART): National Department of Health: Affordable Medicines, EDP-Adult Hospital level. Medicine Review: Dolutegravir in HIV-infected patients commencing first-line antiretroviral therapy, updated 27 July 2021 (including addendum of use of dolutegravir with rifampicin). https://www.knowledgehub.org.za/content/standard-treatment-guidelines-and-essential-medicines-list

Dolutegravir, oral (first-line ART): Rutherford GW, Horvath H. Dolutegravir Plus Two Nucleoside Reverse Transcriptase Inhibitors versus Efavirenz Plus Two Nucleoside Reverse Transcriptase Inhibitors As Initial Antiretroviral Therapy for People with HIV: A Systematic Review. PLoS One. 2016 Oct_13;11(10):e0162775. https://www.ncbi.nlm.nih.gov/pubmed/27736859

Dolutegravir, oral (first-line ART): South African National Department of Health. 2023 Antiretroviral Therapy Clinical Guidelines for the Management of HIV in Adults, Pregnancy and Breastfeeding, Adolescents, Children, Infants and Neonates. April 2023. Accessible at https://knowledgehub.health.gov.za/system/files/elibdownloads/2023-07/National%20ART%20Clinical%20Guideline%20AR%204.5%2020230713%20Version%204%20WEB.pdf

[x] Dolutegravir, oral (first-line ART in pregnancy/ WOCP): National Department of Health: Affordable Medicines, EDP-Adult Hospital level. Medicine Review: Dolutegravir in pregnant women and women of child-bearing potential (WOCP), 17 June 2021.
https://www.knowledgehub.org.za/content/standard-treatment-guidelines-and-essential-medicines-list

Dolutegravir, oral (risk of NTDs): National Department of Health. Notice: Updated guidance of dolutegravir in pregnancy, 29 June 2021 (Reference: 2021/06/29/EDP/01). https://www.knowledgehub.org.za/e-library

[xi] Dolutegravir, oral (first-line ART with concomitant rifampicin): National Department of Health: Affordable Medicines, EDP-Adult Hospital level. Medicine Review: Dolutegravir in HIV-infected patients commencing first-line antiretroviral therapy, updated 27 July 2021 (including addendum of use of dolutegravir with rifampicin).
https://www.knowledgehub.org.za/content/standard-treatment-guidelines-and-essential-medicines-list

Dolutegravir, oral (first-line ART with concomitant rifampicin): Dooley KE, Sayre P, Borland J, Purdy E, Chen S, Song I, et al. Safety, tolerability, and pharmacokinetics of the HIV integrase inhibitor dolutegravir given twice daily with rifampin or once daily with rifabutin: results of a phase 1 study among healthy subjects. J Acquir Immune Defic Syndr 2013; 62(1):21-27. https://pubmed.ncbi.nlm.nih.gov/23075918/

Dolutegravir, oral (first-line ART with concomitant rifampicin): Dooley KE, Kaplan R, Mwelase N, Grinsztejn B, Ticona E, Lacerda M, et al. Dolutegravir-based Antiretroviral Therapy for Patients Coinfected With Tuberculosis and Human Immunodeficiency Virus: A Multicenter, Noncomparative, Open-label, Randomized Trial. Clin Infect Dis 2020; 70(4):549-556. https://pubmed.ncbi.nlm.nih.gov/30918967/

[xii] National Department of Health: Affordable Medicines, EDP-PHC/Adult Hospital level. Medicine Review: Atazanavir/ritonavir vs lopinavir/ritonavir in HIV, 27July2021.
https://www.knowledgehub.org.za/content/standard-treatment-guidelines-and-essential-medicines-list

[xiii] Abacavir: Cruciani M, Mengoli C, Malena M, Serpelloni G, Parisi SG, Moyle G, Bosco O. Virological efficacy of abacavir: systematic review and meta-analysis. J Antimicrob Chemother. 2014 Dec;69(12):3169-80.http://www.ncbi.nlm.nih.gov/pubmed/25074854

[xiv] Dual therapy – dolutegravir/lamivudine: Cahn P, Madero JS, Arribas JR, Antinori A, Ortiz R, Clarke AE, et al; GEMINI Study Team. Dolutegravir plus lamivudine versus dolutegravir plus tenofovir disoproxil fumarate and emtricitabine in antiretroviral-naive adults with HIV-1 infection (GEMINI-1 and GEMINI-2): week 48 results from two multicentre, double-blind, randomised, non-inferiority, phase 3 trials. Lancet. 2019 Jan 12;393(10167):143-155. https://www.ncbi.nlm.nih.gov/pubmed/30420123

Dual therapy – dolutegravir/lamivudine: Hidalgo-Tenorio C, Cortés LL, Gutiérrez A, Santos J, Omar M, Gálvez C, et al. DOLAMA study: Effectiveness, safety and pharmacoeconomic analysis of dual therapy with dolutegravir and lamivudine in virologically suppressed HIV-1 patients. Medicine (Baltimore). 2019 Aug;98(32):e16813. https://www.ncbi.nlm.nih.gov/pubmed/31393412

[xv] South African National Department of Health. 2023 Antiretroviral Therapy Clinical Guidelines for the Management of HIV in Adults, Pregnancy and Breastfeeding, Adolescents, Children, Infants and Neonates. April 2023. Accessible at https://knowledgehub.health.gov.za/system/files/elibdownloads/2023-07/National%20ART%20Clinical%20Guideline%20AR%204.5%2020230713%20Version%204%20WEB.pdf

[xvi] South African National Department of Health. 2023 Antiretroviral Therapy Clinical Guidelines for the Management of HIV in Adults, Pregnancy and Breastfeeding, Adolescents, Children, Infants and Neonates. April 2023. Accessible at https://knowledgehub.health.gov.za/system/files/elibdownloads/2023-07/National%20ART%20Clinical%20Guideline%20AR%204.5%2020230713%20Version%204%20WEB.pdf

[xvii] Dolutegravir, oral (double-dose with concomitant rifampicin): National Department of Health: Affordable Medicines, EDP-Adult Hospital level. Medicine Review: Dolutegravir in HIV-infected patients commencing first-line antiretroviral therapy, updated 27 July 2021 (including addendum of use of dolutegravir with rifampicin).
https://www.knowledgehub.org.za/content/standard-treatment-guidelines-and-essential-medicines-list

Dolutegravir, oral (double-dose with concomitant rifampicin): Dooley KE, Sayre P, Borland J, Purdy E, Chen S, Song I, et al. Safety, tolerability, and pharmacokinetics of the HIV integrase inhibitor dolutegravir given twice daily with rifampin or once daily with rifabutin: results of a phase 1 study among healthy subjects. J Acquir Immune Defic Syndr. 2013 Jan 1;62(1):21-7. https://pubmed.ncbi.nlm.nih.gov/23075918/

Dolutegravir, oral (double-dose with concomitant rifampicin): Dooley KE, Kaplan R, Mwelase N, Grinsztejn B, Ticona E, Lacerda M, et al; International Study of Patients with HIV on Rifampicin ING study group. Dolutegravir-based Antiretroviral Therapy for Patients Coinfected With Tuberculosis and Human Immunodeficiency Virus: A Multicenter, Noncomparative, Open-label, Randomized Trial. Clin Infect Dis. 2020 Feb 3;70(4):549-556. https://pubmed.ncbi.nlm.nih.gov/30918967/

[xviii] South African National Department of Health. 2023 Antiretroviral Therapy Clinical Guidelines for the Management of HIV in Adults, Pregnancy and Breastfeeding, Adolescents, Children, Infants and Neonates. April 2023. Accessible at https://knowledgehub.health.gov.za/system/files/elibdownloads/2023-07/National%20ART%20Clinical%20Guideline%20AR%204.5%2020230713%20Version%204%20WEB.pdf

[xix] Emtricitabine, oral (red cell aplasia adverse drug reaction): Cohen K, Viljoen C, Njuguna C, Maartens G. Emtricitabine-associated red cell aplasia. AIDS. 2019 May 1;33(6):1095-1096. https://www.ncbi.nlm.nih.gov/pubmed/30946164

[xx]Efavirenz, oral (encephalopathy adverse drug reaction): Variava E, Sigauke FR, Norman J, Rakgokong M, Muchichwa P, Mochan A, Maartens G, Martinson NA. Brief Report: Late Efavirenz-Induced Ataxia and Encephalopathy: A Case Series. J Acquir Immune Defic Syndr. 2017 Aug 15;75(5):577-579. https://www.ncbi.nlm.nih.gov/pubmed/28520619

[xxi] Dosing of ART and ADRs: Dosing of ART and ADRs: WHO. Consolidated guidelines on HIV prevention, testing, treatment, service delivery and monitoring: recommendations for a public health approach, July 2021. https://www.who.int/publications/i/item/9789240031593

Dosing of ART and ADRs: South African National Department of Health. 2023 Antiretroviral Therapy Clinical Guidelines for the Management of HIV in Adults, Pregnancy and Breastfeeding, Adolescents, Children, Infants and Neonates. April 2023. Accessible at https://knowledgehub.health.gov.za/system/files/elibdownloads/2023-07/National%20ART%20Clinical%20Guideline%20AR%204.5%2020230713%20Version%204%20WEB.pdf

Dosing of ART and ADRs: South African Medicines Formulary, 14th Edition. Division of Clinical Pharmacology. University of Cape Town, 2022.

Dosing of ART and ADRs: Datapharm Ltd. Electronic medicines compendium (emc). [Internet][Accessed 28 November 2019] https://www.medicines.org.uk/emc/

Dosing of ART (renal impairment): Dosing of ART and ADRs: WHO. Consolidated guidelines on HIV prevention, testing, treatment, service delivery and monitoring: recommendations for a public health approach, July 2021. https://www.who.int/publications/i/item/9789240031593

Dosing of ART (renal impairment): Lucas GM, Ross MJ, Stock PG, Shlipak MG, Wyatt CM, Gupta SK, et al.; HIV Medicine Association of the Infectious Diseases Society of America. Clinical practice guideline for the management of chronic kidney disease in patients infected with HIV: 2014 update by the HIV Medicine Association of the Infectious Diseases Society of America. Clin Infect Dis. 2014 Nov 1;59(9):e96-138. http://www.ncbi.nlm.nih.gov/pubmed/25234519

Dosing of ART (renal impairment): Meintjes G, Moorhouse MA, Carmona S, Davies N, Dlamini S, van Vuuren C, Manzini T, et al. Adult antiretroviral therapy guidelines 2017. South Afr J HIV Med. 2017 Jul 15;18(1):776. doi: 10.4102/sajhivmed.v18i1.776. https://pubmed.ncbi.nlm.nih.gov/29568644/

[xxii] ART-rifampicin drug interaction: WHO. Consolidated guidelines on HIV prevention, testing, treatment, service delivery and monitoring: recommendations for a public health approach, July 2021. https://www.who.int/publications/i/item/9789240031593

ART-rifampicin drug interaction: South African National Department of Health. 2023 Antiretroviral Therapy Clinical Guidelines for the Management of HIV in Adults, Pregnancy and Breastfeeding, Adolescents, Children, Infants and Neonates. April 2023. Accessible at https://knowledgehub.health.gov.za/system/files/elibdownloads/2023-07/National%20ART%20Clinical%20Guideline%20AR%204.5%2020230713%20Version%204%20WEB.pdf

[xxiii]Rifabutin: Zhang J, Zhu L, Stonier M, Coumbis J, Xu X, Wu Y, Arikan D, Farajallah A, Bertz R. Determination of rifabutin dosing regimen when administered in combination with ritonavir-boosted atazanavir. J Antimicrob Chemother. 2011 Sep;66(9):2075-82. http://www.ncbi.nlm.nih.gov/pubmed/21712242

Rifabutin (dosing): Lan NT, Thu NT, Barrail-Tran A, Duc NH, Lan NN, Laureillard D, et al. Randomised pharmacokinetic trial of rifabutin with lopinavir/ritonavir-antiretroviral therapy in patients with HIV-associated tuberculosis in Vietnam. PLoS One. 2014 Jan 22;9(1):e84866. http://www.ncbi.nlm.nih.gov/pubmed/24465443

Rifabutin (dosing): Ramachandran G, Bhavani PK, Hemanth Kumar AK, Srinivasan R, Raja K, Sudha V, Venkatesh S, Chandrasekaran C, Swaminathan S. Pharmacokinetics of rifabutin during atazanavir/ritonavir co-administration in HIV-infected TB patients in India. Int J Tuberc Lung Dis. 2013 Dec;17(12):1564-8. https://www.ncbi.nlm.nih.gov/pubmed/24200269

[xxiv] Drug interactions with dolutegravir: WHO. Consolidated guidelines on HIV prevention, testing, treatment, service delivery and monitoring: recommendations for a public health approach, July 2021. https://www.who.int/publications/i/item/9789240031593

Drug interactions with dolutegravir: South African National Department of Health. 2023 Antiretroviral Therapy Clinical Guidelines for the Management of HIV in Adults, Pregnancy and Breastfeeding, Adolescents, Children, Infants and Neonates. April 2023. Accessible at https://knowledgehub.health.gov.za/system/files/elibdownloads/2023-07/National%20ART%20Clinical%20Guideline%20AR%204.5%2020230713%20Version%204%20WEB.pdf

[xxv] Atazanavir-PPI/H2-anatagonist interaction: University of Liverpool HIV Drug Interaction online tool. https://www.hiv-druginteractions.org/checker

Atazanavir-PPI interaction: Khanlou H, Farthing C. Co-administration of atazanavir with proton-pump inhibitors and H2 blockers. J Acquir Immune Defic Syndr. 2005 Aug 1;39(4):503. https://www.ncbi.nlm.nih.gov/pubmed/16010179

Atazanavir-PPI interaction: European Medicines Agency. Public Statement: Important new pharmacokinetic data demonstrating that REYATAZ(atazanavir sulfate) combined with NORVIR (ritonavir) and omeprazole should not be co-administered, 21 December 2004. https://www.ema.europa.eu/en/documents/public-statement/important-new-pharmacokinetic-data-demonstrating-reyataz-atazanavir-sulfate-combined-norvir_en.pdf

[xxvi] Screen for Cryptococcus antigen: South African National Department of Health. 2023 Antiretroviral Therapy Clinical Guidelines for the Management of HIV in Adults, Pregnancy and Breastfeeding, Adolescents, Children, Infants and Neonates. April 2023. Accessible at https://knowledgehub.health.gov.za/system/files/elibdownloads/2023-07/National%20ART%20Clinical%20Guideline%20AR%204.5%2020230713%20Version%204%20WEB.pdf

[xxvii]Urine dipstick: Han TM, Naicker S, Ramdial PK, Assounga AG. A cross-sectional study of HIV-seroposistive patients with varying degrees of proteinuria in South Africa. Kidney Int. 2006 Jun;69(12):2243-50. http://www.ncbi.nlm.nih.gov/pubmed/16672914

[xxviii] LAM urine testing (DS-TB): Bjerrum S, Schiller I, Dendukuri N, Kohli M, Nathavitharana RR, Zwerling AA,

et al. Lateral flow urine lipoarabinomannan assay for detecting active tuberculosis in people living with HIV. Cochrane Database Syst Rev. 2019 Oct 21;10:CD011420. https://www.ncbi.nlm.nih.gov/pubmed/31633805

LAM urine testing (DS-TB): National Department of Health. Guidance on the use of the lipoarabinomannan lateral flow assay (LF-LAM) for the diagnosis of tuberculosis in people living with HIV, July 2017. https://www.knowledgehub.org.za/

[xxix]Abacavir: South African Medicines Formulary, 14th Edition. Division of Clinical Pharmacology. University of Cape Town, 2022

[xxx]Management of drug-induced liver injury: Jong E, Conradie F, Berhanu R, Black A, John MA, Meintjes G, Menezes C. Consensus Statement: Management of drug-induced liver injury in HIV-positive patients treated for TB. S Afri HIV Med 2013;14(3): 113-119.http://www.sajhivmed.org.za/index.php/hivmed/article/view/63

Management of drug-induced liver injury: Sharma SK, Singla R, Sarda P, Mohan A, Makharia G, Jayaswal A, Sreenivas V, Singh S. Safety of 3 different reintroduction regimens of antituberculosis drugs after development of antituberculosis treatment-induced hepatotoxicity. Clin Infect Dis. 2010 Mar 15;50(6):833-9. https://www.ncbi.nlm.nih.gov/pubmed/20156055

[xxxi]Prednisone, oral (TB-IRIS on ART): Meintjes G, Stek C, Blumenthal L, Thienemann F, Schutz C, Buyze J, et al; PredART Trial Team. Prednisone for the Prevention of Paradoxical Tuberculosis-Associated IRIS. N Engl J Med. 2018 Nov 15;379(20):1915-1925. https://www.ncbi.nlm.nih.gov/pubmed/30428290

[xxxii]TB preventive therapy (therapeutic class): Affordable Medicines, EDP- Adult Hospital level. Medicine Review: Isoniazid TB prophylaxis in PLHIV, November 2018. https://www.knowledgehub.org.za/content/standard-treatment-guidelines-and-essential-medicines-list

TB preventive therapy (therapeutic class): Rangaka MX, Wilkinson RJ, Boulle A, Glynn JR, Fielding K, van Cutsem G, et al. Isoniazid plus antiretroviral therapy to prevent tuberculosis: a randomised double-blind placebo-controlled trial. Lancet 2014;384(9944):682-90. http://www.ncbi.nlm.nih.gov/pubmed/24835842

TB preventive therapy (therapeutic class): Affordable Medicines, EDP- Adult Hospital level. Medicine Review: Rifapentine (3HP) as TPT in PLHIV, November 2019. https://www.knowledgehub.org.za/content/standard-treatment-guidelines-and-essential-medicines-list

TB preventive therapy (therapeutic class): Affordable Medicines, EDP-Adult Hospital level. Medicine Review: Rifapentine (3HP) as TPT in PLHIV on DTG-regimens, November 2019. https://www.knowledgehub.org.za/content/standard-treatment-guidelines-and-essential-medicines-list

[xxxiii] Rifapentine-containing regimen (3HP): Affordable Medicines, EDP- Adult Hospital level. Medicine Review: Rifapentine (3HP) as TPT in PLHIV, November 2019. https://www.knowledgehub.org.za/content/standard-treatment-guidelines-and-essential-medicines-list

Rifapentine-containing regimen (3HP): Affordable Medicines, EDP-Adult Hospital level. Medicine Review: Rifapentine (3HP) as TPT in PLHIV on DTG-regimens, November 2019. https://www.knowledgehub.org.za/content/standard-treatment-guidelines-and-essential-medicines-list

[xxxiv] IPT in pregnancy: Affordable Medicines, EDP- Adult Hospital level. Medicine Review: Evidence review: IPT in pregnancy_v1.2_15 April 2024_final approved. https://www.knowledgehub.org.za/content/standard-treatment-guidelines-and-essential-medicines-list

[xxxv]Cotrimoxazole, oral (pregnancy): National Department of Health: Affordable Medicines, EDP-Adult Hospital level. Evidence summary: Is co-trimoxazole safe to use in pregnancy, March2024. https://www.knowledgehub.org.za/content/standard-treatment-guidelines-and-essential-medicines-list

Cotrimoxazole, oral (pregnancy): WHO. Consolidated guidelines on HIV prevention, testing, treatment, service delivery and monitoring: recommendations for a public health approach, July 2021. https://www.who.int/publications/i/item/9789240031593

[xxxvi]Cotrimoxazole, oral: Grimwade K, Swingler, G. Cotrimoxazole prophylaxis for opportunistic infections in adults with HIV. Cochrane Database Syst Rev. 2003;(3):CD003108. http://www.ncbi.nlm.nih.gov/pubmed/12917946

Cotrimoxazole, oral: South African National Department of Health. 2023 Antiretroviral Therapy Clinical Guidelines for the Management of HIV in Adults, Pregnancy and Breastfeeding, Adolescents, Children, Infants and Neonates. April 2023. Accessible at https://knowledgehub.health.gov.za/system/files/elibdownloads/2023-07/National%20ART%20Clinical%20Guideline%20AR%204.5%2020230713%20Version%204%20WEB.pdf

[xxxvii]Cotrimoxazole, oral (criteria for discontinuation): WHO. Consolidated guidelines on HIV prevention, testing, treatment, service delivery and monitoring: recommendations for a public health approach, July 2021. https://www.who.int/publications/i/item/9789240031593

Cotrimoxazole, oral (criteria for discontinuation): South African National Department of Health. 2023 Antiretroviral Therapy Clinical Guidelines for the Management of HIV in Adults, Pregnancy and Breastfeeding, Adolescents, Children, Infants and Neonates. April 2023. Accessible at https://knowledgehub.health.gov.za/system/files/elibdownloads/2023-07/National%20ART%20Clinical%20Guideline%20AR%204.5%2020230713%20Version%204%20WEB.pdf

[xxxviii]CrAg screening (CD4 < 100 cells/mm^3): Meya DB, Manabe YC, Castelnuovo B, Cook BA, Elbireer AM, Kambugu A, et al. Cost-effectiveness of serum cryptococcal antigen screening to prevent deaths among HIV-infected persons with a CD4+ cell count < or = 100 cells/microL who start HIV therapy in resource-limited settings. Clin Infect Dis. 2010 Aug 15;51(4):448-55. http://www.ncbi.nlm.nih.gov/pubmed/20597693

CrAg screening (CD4 < 100 cells/mm^3): Ford N, Shubber Z, Jarvis JN, Chiller T, Greene G, Migone C, Vitoria M, Doherty M, Meintjes G. CD4 Cell Count Threshold for Cryptococcal Antigen Screening of HIV-Infected Individuals: A

Systematic Review and Meta-analysis. Clin Infect Dis. 2018 Mar 4;66(suppl_2):S152-S159. https://pubmed.ncbi.nlm.nih.gov/29514236/

CrAg screening (CD4 < 100 cells/mm^3): WHO. Consolidated guidelines on HIV prevention, testing, treatment, service delivery and monitoring: recommendations for a public health approach, July 2021. https://www.who.int/publications/i/item/9789240031593

[xxxix] ART (delayed): Makadzange AT, Ndhlovu CE, Takarinda K, Reid M, Kurangwa M, Gona P, Hakim JG. Early versus delayed initiation of antiretroviral therapy for concurrent HIV infection and cryptococcal meningitis in sub-saharan Africa. Clin Infect Dis. 2010 Jun 1;50(11):1532-8.http://www.ncbi.nlm.nih.gov/pubmed/20415574

ART (delayed): WHO. Consolidated guidelines on HIV prevention, testing, treatment, service delivery and monitoring: recommendations for a public health approach, July 2021. https://www.who.int/publications/i/item/9789240031593

ART (delayed): Govender NP, Meintjes G, Mangena P, Nel J, Potgieter S, Reddy D, et al. Southern African HIV Clinicians Society guideline for the prevention, diagnosis and management of cryptococcal disease among HIV-infected persons: 2019 update. S Afr J HIV Med 2019;20(1):a1030. https://doi.org/10.4102/sajhivmed.v20i1.1030

[xl]Fluconazole, oral (cryptococcosis): WHO. Consolidated guidelines on HIV prevention, testing, treatment, service delivery and monitoring: recommendations for a public health approach, July 2021. https://www.who.int/publications/i/item/9789240031593

Fluconazole, oral (cryptococcosis): Govender NP, Meintjes G, Mangena P, Nel J, Potgieter S, Reddy D, et al. Southern African HIV Clinicians Society guideline for the prevention, diagnosis and management of cryptococcal disease among HIV-infected persons: 2019 update. S Afr J HIV Med 2019;20(1):a1030. https://doi.org/10.4102/sajhivmed.v20i1.1030

Fluconazole, oral (cryptococcosis): NICD data on file.

[xli] Fluconazole, oral (pregnancy): Mølgaard-Nielsen D, Pasternak B, Hviid A. Use of oral fluconazole during pregnancy and the risk of birth defects. N Engl J Med. 2013 Aug 29;369(9):830-9. http://www.ncbi.nlm.nih.gov/pubmed/23984730

Fluconazole, oral (pregnancy): Mølgaard-Nielsen D, Svanström H, Melbye M, Hviid A, Pasternak B. Association Between Use of Oral Fluconazole During Pregnancy and Risk of Spontaneous Abortion and Stillbirth. JAMA. 2016 Jan 5;315(1):58-67. http://www.ncbi.nlm.nih.gov/pubmed/26746458

Fluconazole, oral (pregnancy): Govender NP, Meintjes G, Mangena P, Nel J, Potgieter S, Reddy D, et al. Southern African HIV Clinicians Society guideline for the prevention, diagnosis and management of cryptococcal disease among HIV-infected persons: 2019 update. S Afr J HIV Med 2019;20(1):a1030. https://doi.org/10.4102/sajhivmed.v20i1.1030

[xlii] Fluconazole, oral (breastfeeding): South African Medicines Formulary, 14th Edition. Division of Clinical Pharmacology. University of Cape Town, 2022.

Fluconazole, oral (breastfeeding): Govender NP, Meintjes G, Mangena P, Nel J, Potgieter S, Reddy D, et al. Southern African HIV Clinicians Society guideline for the prevention, diagnosis and management of cryptococcal disease among HIV-infected persons: 2019 update. S Afr J HIV Med 2019;20(1):a1030. https://doi.org/10.4102/sajhivmed.v20i1.1030

[xliii] Liposomal amphotericin: National Department of Health: Affordable Medicines, EDP-Adult Hospital level. Medicine Review: Liposomal Amphotericin B_ cryptococcal meningitis_Adults Review_Update_23 January 2024_final approved.

[xliv]Flucytosine, oral: National Department of Health: Affordable Medicines, EDP-Adult Hospital level. Medicine Review: Flucytosine for cryptococcal meningitis, 15 November 2018. https://www.knowledgehub.org.za/e-library

Flucytosine, oral: National Department of Health: Affordable Medicines, EDP-Adult Hospital level. Health economic and budget impact analysis: Flucytosine as induction therapy in the treatment of cryptococcal meningitis in HIV infected adults, June 2019. https://www.knowledgehub.org.za/e-library

https://www.nejm.org/doi/full/10.1056/NEJMoa2111904

Flucytosine, oral: Tenforde MW, Shapiro AE, Rouse B, Jarvis JN, Li T, Eshun-Wilson I, Ford N. Treatment for HIV-associated cryptococcal meningitis. Cochrane Database Syst Rev. 2018 Jul 25;7(7):CD005647. https://pubmed.ncbi.nlm.nih.gov/30045416/

Flucytosine, oral: Miot J, Leong T, Takuva S, Parrish A, Dawood H. Cost-effectiveness analysis of flucytosine as induction therapy in the treatment of cryptococcal meningitis in HIV-infected adults in South Africa. BMC Health Serv Res. 2021 Apr 6;21(1):305. https://pubmed.ncbi.nlm.nih.gov/33823842/

[xlv]Fluconazole, oral: Govender NP, Meintjes G, Mangena P, Nel J, Potgieter S, Reddy D, et al. Southern African HIV Clinicians Society guideline for the prevention, diagnosis and management of cryptococcal disease among HIV-infected persons: 2019 update

[xlvi]Fluconazole, oral (induction phase): Tenforde MW, Shapiro AE, Rouse B, Jarvis JN, Li T, Eshun-Wilson I et al. Treatment for HIVassociated cryptococcal meningitis. Cochrane Database Syst Rev. 2018;7;CD005647. https://pubmed.ncbi.nlm.nih.gov/30045416/

Fluconazole, oral (induction phase): WHO. Consolidated guidelines on HIV prevention, testing, treatment, service delivery and monitoring: recommendations for a public health approach, July 2021. https://www.who.int/publications/i/item/9789240031593

Fluconazole, oral (induction phase): Govender NP, Meintjes G, Mangena P, Nel J, Potgieter S, Reddy D, et al. Southern African HIV Clinicians Society guideline for the prevention, diagnosis and management of cryptococcal disease among HIV-infected persons: 2019 update. S Afr J HIV Med 2019;20(1):a1030. https://doi.org/10.4102/sajhivmed.v20i1.1030

[xlvii]Fluconazole, oral (consolidation phase): WHO. Consolidated guidelines on HIV prevention, testing, treatment, service delivery and monitoring: recommendations for a public health approach, July 2021. https://www.who.int/publications/i/item/9789240031593

Fluconazole, oral (consolidation phase): Govender NP, Meintjes G, Mangena P, Nel J, Potgieter S, Reddy D, et al. Southern African HIV Clinicians Society guideline for the prevention, diagnosis and management of cryptococcal disease among HIV-infected persons: 2019 update. S Afr J HIV Med 2019;20(1):a1030. https://doi.org/10.4102/sajhivmed.v20i1.1030

[xlviii]Fluconazole, oral (maintenance phase): WHO. Consolidated guidelines on HIV prevention, testing, treatment, service delivery and monitoring: recommendations for a public health approach, July 2021. https://www.who.int/publications/i/item/9789240031593

Fluconazole, oral (maintenance phase): Bozzette SA, Larsen RA, Chiu J, Leal MA, Jacobsen J, Rothman P, Robinson P, Gilbert G, McCutchan JA, Tilles J, et al. A placebo-controlled trial of maintenance therapy with fluconazole after treatment of cryptococcal meningitis in the acquired immunodeficiency syndrome. California Collaborative Treatment Group. N Engl J Med. 1991 Feb 28;324(9):580-4. https://pubmed.ncbi.nlm.nih.gov/1992319/

Fluconazole, oral (maintenance phase): Powderly WG, Saag MS, Cloud GA, Robinson P, Meyer RD, Jacobson JM, Graybill JR, Sugar AM, McAuliffe VJ, Follansbee SE, et al. A controlled trial of fluconazole or amphotericin B to prevent relapse of cryptococcal meningitis in patients with the acquired immunodeficiency syndrome. The NIAID AIDS Clinical Trials Group and Mycoses Study Group. N Engl J Med. 1992 Mar 19;326(12):793-8. https://pubmed.ncbi.nlm.nih.gov/1538722/

Fluconazole, oral (maintenance phase): Govender NP, Meintjes G, Mangena P, Nel J, Potgieter S, Reddy D, et al. Southern African HIV Clinicians Society guideline for the prevention, diagnosis and management of cryptococcal disease among HIV-infected persons: 2019 update. S Afr J HIV Med 2019;20(1):a1030. https://doi.org/10.4102/sajhivmed.v20i1.1030

[xlix] ART (delayed): Makadzange AT, Ndhlovu CE, Takarinda K, Reid M, Kurangwa M, Gona P, Hakim JG. Early versus delayed initiation of antiretroviral therapy for concurrent HIV infection and cryptococcal meningitis in sub-saharan Africa. Clin Infect Dis. 2010 Jun 1;50(11):1532-8.http://www.ncbi.nlm.nih.gov/pubmed/20415574

ART (delayed): WHO. Consolidated guidelines on HIV prevention, testing, treatment, service delivery and monitoring: recommendations for a public health approach, July 2021. https://www.who.int/publications/i/item/9789240031593

[l]Steroids and HIV-associated Cryptococcal Meningitis Treatment: Beardsley J, Wolbers M, Kibengo FM, Ggayi AB, Kamali A, Cuc NT, et al. Adjunctive dexamethasone in HIV-associated cryptococcal meningitis. N Engl J Med 2016;374:542-54. https://www.ncbi.nlm.nih.gov/pubmed/26863355

[li]Azithromycin: Dunne M, Fessel J, Kumar P, Dickenson G, Keiser P, Boulos M, Mogyros M, White Jr AC, Cahn P, O'Connor M, Lewi D, Green S, Tilles J, Hicks C, Bissett J, Schneider MM, Benner R. A randomized, double-blind trial comparing azithromycin and clarithromycin in the treatment of disseminated Mycobacterium avium infection in patients with human immunodeficiency virus. Clin Infect Dis. 2000 Nov;31(5):1245-52. Erratum in: Clin Infect Dis 2001 May 1;32(9):1386. http://www.ncbi.nlm.nih.gov/pubmed/11073759

Azithromycin: Ward TT, Rimland D, Kauffman C, Huycke M, Evans TG, Heifets L. Randomized, open-label trial of azithromycin plus ethambutol vs. clarithromycin plus ethambutol as therapy for Mycobacterium avium complex bacteremia in patients with human immunodeficiency virus infection. Veterans Affairs HIV Research Consortium. Clin Infect Dis. 1998 Nov;27(5):1278-85. http://www.ncbi.nlm.nih.gov/pubmed/9827282

[lii] Dolutegravir-based PEP regimen: WHO. Consolidated guidelines on HIV prevention, testing, treatment, service delivery and monitoring: recommendations for a public health approach, July 2021. https://www.who.int/publications/i/item/9789240031593

Dolutegravir-based PEP regimen: McAllister JW, Towns JM, McNulty A, Pierce AB, Foster R, Richardson R, et al. Dolutegravir with tenofovir disoproxil fumarate-emtricitabine as HIV postexposure prophylaxis in gay and bisexual men. AIDS. 2017;31(9):1291–5. https://www.ncbi.nlm.nih.gov/pubmed/28301425

Dolutegravir-based PEP regimen National Department of Health. National Clinical Guidelines of post-exposure prophylaxis (PEP) in occupational and non-occupational exposures, December 2020. https://www.knowledgehub.org.za/elibrary/national-clinical-guidelines-post-exposure-prophylaxis-pep-occupational-and-non

[liii]Protease-inhibitor- based PEP regimen: Ford N, Shubber Z, Calmy A, Irvine C, Rapparini C, Ajose O, et al. Choice of antiretroviral drugs for postexposure prophylaxis for adults and adolescents: A systematic review. Clinical Infectious Diseases. 2015;60 Suppl 3:S170–6. https://www.ncbi.nlm.nih.gov/pubmed/25972499

Protease-inhibitor- based PEP regimen: National Department of Health. National Clinical Guidelines of post-exposure prophylaxis (PEP) in occupational and non-occupational exposures, December 2020. https://www.knowledgehub.org.za/elibrary/national-clinical-guidelines-post-exposure-prophylaxis-pep-occupational-and-non

[liv]Hepatitis B protocol (PEP): National Department of Health. National Clinical Guidelines of post-exposure prophylaxis (PEP) in occupational and non-occupational exposures, December 2020. https://www.knowledgehub.org.za/elibrary/national-clinical-guidelines-post-exposure-prophylaxis-pep-occupational-and-non

[lv]Monitoring in occupational exposures: National Department of Health. National Clinical Guidelines of post-exposure prophylaxis (PEP) in occupational and non-occupational exposures, December 2020. https://www.knowledgehub.org.za/elibrary/national-clinical-guidelines-post-exposure-prophylaxis-pep-occupational-and-non

[lvi]Copper IUD (emergency contraception): Turok DK, Jacobson JC, Dermish AI, Simonsen SE, Gurtcheff S, McFadden M, Murphy PA. Emergency contraception with a copper IUD or oral levonorgestrel: an observational study of 1-year pregnancy rates. Contraception. 2014 Mar;89(3):222-8. https://pubmed.ncbi.nlm.nih.gov/24332433/

Copper IUD (emergency contraception): FSRH Guideline (April 2019) Overweight, Obesity and Contraception. BMJ Sex Reprod Health. 2019 Apr;45(Suppl 2):1-69. https://pubmed.ncbi.nlm.nih.gov/31053605/
[lvii]Levonorgestrel 1.5 mg oral (emergency contraception): Shen J, Che Y, Showell E, Chen K, Cheng L. Interventions for emergency contraception. Cochrane Database Syst Rev. 2019 Jan 20;1(1):CD001324. https://pubmed.ncbi.nlm.nih.gov/30661244/
[lviii]Levonorgesterol, oral - emergency contraception (double dose): Carten ML, Kiser JJ, Kwara A, Mawhinney S, Cu-Uvin S. Pharmacokinetic interactions between the hormonal emergency contraception, levonorgestrel (Plan B), and Efavirenz. Infect Dis Obstet Gynecol. 2012;2012:137192. http://www.ncbi.nlm.nih.gov/pubmed/22536010
Levonorgesterol, oral - emergency contraception (double dose): Tittle V, Bull L, Boffito M, Nwokolo N. Pharmacokinetic and pharmacodynamic drug interactions between antiretrovirals and oral contraceptives. ClinPharmacokinet. 2015 Jan;54(1):23-34. http://www.ncbi.nlm.nih.gov/pubmed/25331712
Levonorgesterol, oral - emergency contraception (double dose): Jatlaoui TC and Curtis KM. Safety and effectiveness data for emergency contraceptive pills among women with obesity: a systematic review. Contraception 94 (2016) 605–611. https://www.ncbi.nlm.nih.gov/pubmed/27234874
Levonorgesterol, oral - emergency contraception (double dose): FSRH Guideline (April 2019) Overweight, Obesity and Contraception. BMJ Sex Reprod Health. 2019 Apr;45(Suppl 2):1-69. https://pubmed.ncbi.nlm.nih.gov/31053605/
[lix] Metoclopramide, oral: National Department of Health, Essential Drugs Programme: Primary Health Care STGs and EML, 2020. http://www.health.gov.za/
[lx]STI prophylaxis: Workowski KA, Bachmann LH, Chan PA, Johnston CM, Muzny CA, Park I, Reno H, Zenilman JM, Bolan GA. Sexually Transmitted Infections Treatment Guidelines, 2021. MMWR Recomm Rep. 2021 Jul 23;70(4):1-187. https://pubmed.ncbi.nlm.nih.gov/34292926/
[lxi]Non-occupational PEP: National Department of Health. National Clinical Guidelines of post-exposure prophylaxis (PEP) in occupational and non-occupational exposures, December 2020. https://www.knowledgehub.org.za/elibrary/national-clinical-guidelines-post-exposure-prophylaxis-pep-occupational-and-non

CHAPTER 11

SURGICAL ANTIBIOTIC PROPHYLAXIS

GENERAL PRINCIPLES

» Prophylactic antibiotic therapy reduces the risk of surgical site infection.
» The need for surgical antibiotic prophylaxis depends on the nature of the expected wound from the procedure.
» Wounds that are expected to be clean (defined as no inflammation encountered; and the respiratory, alimentary, genital, or uninfected urinary tracts were not entered) generally do not require antibiotic prophylaxis, except where the consequences of surgical site infection could be severe (e.g. joint replacement in orthopaedic surgery).
» Antibiotic prophylaxis is indicated for procedures with clean-contaminated wounds (defined as entering the respiratory, alimentary, genital, or urinary tracts under controlled conditions; and without unusual contamination). *LoE:III[i]*
» A course of antibiotic treatment, not antibiotic prophylaxis, is required for procedures with contaminated wounds (defined as fresh open accidental wounds, or operations with major breaks in sterile technique), or dirty or infected wounds (defined as old traumatic wounds with retained devitalized tissue; and those that involve existing clinical infection or perforated viscera). *LoE:III[ii]*
(See chapter 20: Emergencies and injuries for antibiotic treatment).
» The antibiotic of choice should be active against Gram positive organisms, notably *Staphylococcus aureus*, which is the commonest cause of surgical site infections, with additional cover for other common pathogens according to the surgical site (e.g. anaerobic bacteria for GIT surgery).
» Give prophylaxis at induction. *LoE:III[iii]*
» If a tourniquet is used at the site of surgery, administer the entire antibiotic dose before the tourniquet is inflated. *LoE:III[iv]*
» Implement perioperative glycaemic control and use blood glucose target levels less than 11.1 mmol/L in patients with and without diabetes. *LoE:III[v]*
» Maintain perioperative normothermia. *LoE:III[vi]*
» Antibiotic prophylaxis should be used in conjunction with good pre-, intra-, and post-operative infection prevention strategies.
» Advise patient to shower or bathe with soap or antiseptic agent on at least the night before the procedure. *LoE:III[vii]*

» Do not remove hair preoperatively unless the hair at or around the incision site will interfere with the operation. If hair removal is necessary, remove immediately before the operation, with clippers.

LoE:I[viii]

DOSAGE RECOMMENDATIONS:

- Cefazolin, IV (A).
  - <60 kg: 1 g
  - 60–120 kg and BMI ≤35: 2 g
  - ≥120 kg or BMI >35: 3 g

LoE:III[ix]

Pregnant women:

  - <60 kg: 1 g
  - 60–100 kg: 2 g
  - >100 kg: 3 g

LoE:III[x]

- Metronidazole, IV, 500 mg (A).
- Azithromycin, IV, 500 mg (W).
- Gentamicin, IV, 6 mg/kg (A) (See Appendix II, for guidance on prescribing).
- Clindamycin, IV, 600 mg (A).

In most instances a single antibiotic dose prior to the procedure is sufficient for prophylaxis. Postoperative antimicrobial administration is not recommended for most surgeries as this selects for antimicrobial resistance.

LoE:I[xi]

» Additional intra-operative doses should be administered in circumstances of significant blood loss (>1500 mL) in order to ensure an adequate antimicrobial level until wound closure.

LoE:III[xii]

» With prolonged procedures, antibiotics are required to be re-dosed (i.e. >4 hours for cefazolin; >8 hours for metronidazole; > 6 hours for clindamycin and gentamicin).

LoE:III[xiii]

ANTIBIOTIC PROPHYLAXIS

TYPE OF SURGERY	ANTIBIOTIC RECOMMENDED	
	• *Cefazolin, IV*	• *Cefazolin, IV* (A) ***PLUS***
Orthopaedic surgery	Primary total hip/ total knee replacement; internal fixation of hip; spinal procedures; open reduction and internal fixation of fractures; insertion of prostheses, screws, plates, lower limb amputation, etc.	
Gastrointestinal surgery	Gastric/ duodenal/ oesophageal hernia repair.	Biliary, colorectal, manipulation of viscera, appendicectomy, division of adhesions, exploratory laparotomy: **ADD** • Metronidazole, IV (A).
Thoracic surgery(specialist)		Pneumonectomy/ lobectomy: **ADD** • Metronidazole, IV (A).
Cardiac surgery (specialist)	Coronary artery bypass surgery/ routine cardiac valve surgery (continue cefazolin, IV, 8 hourly for 24 hours); cardiac device insertion (pacemaker implantation).	
Vascular surgery (specialist) (Prophylaxis is **not** recommended for other clean procedures).	Vascular reconstruction: abdominal aorta, groin incision (continue 8 hourly for 24 hours); AV fistula formation; and ligation of varicose veins.	Lower limb amputation: **ADD** • Metronidazole, IV (A).
Urology	Clean procedures	Clean-contaminated procedures: **ADD**

		• Metronidazole, IV A.
Plastic and reconstructive surgery (Prophylaxis is **not** recommended for clean bone or soft tissue surgery).	Craniotomy procedures.	
Otorhinolaryngology/ head and neck surgery (Prophylaxisis **not** recommended for other procedures such as tonsillectomy, sinus procedures, etc.).	No incision through the oropharyngeal mucosa.	With incision through the oropharyngeal mucosa: **ADD** • Metronidazole, IV A.
Obstetrics/ gynaecology (Prophylaxis is **not** recommended for early suction termination).		Hysterectomy, laparotomy procedures, vaginal repair: **ADD** • Metronidazole, IV A.
		Caesarean delivery: **ADD** • Azithromycin, IV W.
Neurosurgery (Prophylaxis is **not** recommended for other minor clean procedures).	Craniotomy; CSF shunt/drain; laminectomy.	
Endoscopic gastrointestinal procedures (Prophylaxis is **not** recommended for all other procedures, with or without biopsy).	Percutaneous endoscopic gastrostomy insertion/revision.	
General Surgery (Prophylaxis is **not** recommended for uncomplicated clean procedures or clean excision procedures i.e. wound revision, excision of scar tissue, etc.).	Clean contaminated procedures (mastectomy, node biopsy, etc.), splenectomy.	

LoE:I[xiv]

Beta lactam allergies: Avoid beta-lactam antimicrobials in patients with a history of anaphylaxis, bronchospasm, urticaria, or angioedema after exposure to one of these agents.

- Clindamycin, IV A.

ADD

- Gentamicin, IV A **for the procedures listed below:** (See Appendix II, for guidance on prescribing).

» Gastrointestinal surgery, urology procedures (clean-contaminated), and obstetric/gynaecological surgery (hysterectomy, laparotomy procedures, vaginal repair).

Note: Clindamycin has good coverage against Gram positive organisms and anaerobes, so the addition of metronidazole is unnecessary.

LoE:III[xv]

Ophthalmic surgery:

- Chloramphenicol 0.5% ophthalmic drops A, instil 1 drop 2–4 hourly for 24 hours prior to surgery.

SPECIAL CONSIDERATIONS

» Elective splenectomy patients should be vaccinated at least 14 days prior to surgery. If splenectomy was urgent, or if vaccination was omitted before elective splenectomy, vaccinate at least 14 days post-splenectomy.

» The following vaccines should be administered: *LoE:II*[xvi]

VACCINE	SCHEDULE
• Polyvalent pneumococcal vaccine, 0.5 mL, SC.	○ PCV13, SC, 2 weeks before surgery. ○ PPS23, SC, 8 weeks later. ○ Revaccinate with PPS23 after 5 years and then at 65 years. *LoE:II*[xvii]
• Haemophilus influenza type B, 0.5 mL, intramuscular.	–
• Meningococcal polysaccharide vaccine ($ACW_{135}Y$), 0.5 mL, SC	Revaccinate every 5 years.
• Influenza vaccine, 0.5 mL, IM.	Revaccinate annually.

LoE:III[xviii]

PROCESS MEASURES

Measure the percentage of procedures in which antimicrobial prophylaxis was appropriately provided.

These include:

» Correct type of antibiotic.
» Correct dose.
» Administration of the antibiotic(s) within 1 hour before incision.
» Not continuing the antibiotic(s) after surgery (except for 24 hours for cardiac and selected vascular procedures).

References:

[i] Surgical antibiotic prophylaxis: Centers for Disease Control and Prevention. Procedure-associated Module. Surgical Site Infection (SSI) Event. [Online] [Published April 2015; accessed December 2015] http://www.cdc.gov/nhsn/PDFs/pscManual/9pscSSIcurrent.pdf

[ii] Surgical antibiotic prophylaxis: Centers for Disease Control and Prevention. Procedure-associated Module. Surgical Site Infection (SSI) Event. [Online] [Published April 2015; accessed December 2015] http://www.cdc.gov/nhsn/PDFs/pscManual/9pscSSIcurrent.pdf

[iii] Surgical antibiotic prophylaxis (timing): Bratzler DW, Dellinger EP, Olsen KM, Perl TM, Auwaerter PG, Bolon MK, Fish DN, Napolitano LM, Sawyer RG, Slain D, Steinberg JP, Weinstein RA; American Society of Health-System Pharmacists; Infectious Disease Society of America; Surgical Infection Society; Society for Healthcare Epidemiology of America. Clinical practice guidelines for antimicrobial prophylaxis in surgery. Am J Health Syst Pharm. 2013 Feb 1;70(3):195-283. https://www.ncbi.nlm.nih.gov/pubmed/23327981

Surgical antibiotic prophylaxis (timing):Burke JP. Maximizing appropriate antibiotic prophylaxis for surgical patients:an update from LDS Hospital, Salt Lake City. ClinInfect Dis. 2001 Sep 1;33Suppl2:S78-83. http://www.ncbi.nlm.nih.gov/pubmed/11486303

Surgical antibiotic prophylaxis (timing): Bratzler DW, Houck PM, Richards C, Steele L, Dellinger EP, Fry DE, Wright C, Ma A, Carr K, Red L. Use of antimicrobial prophylaxis for major surgery: baseline results from the National Surgical Infection Prevention Project. Arch Surg. 2005 Feb;140(2):174-82. http://www.ncbi.nlm.nih.gov/pubmed/11486303

Surgical antibiotic prophylaxis (timing): van Kasteren ME, Manniën J, Ott A, Kullberg BJ, de Boer AS, Gyssens IC. Antibiotic prophylaxis and the risk of surgical site infections following total hip arthroplasty: timely administration is the most important factor. Clin Infect Dis. 2007 Apr 1;44(7):921-7. http://www.ncbi.nlm.nih.gov/pubmed/17342642

Surgical antibiotic prophylaxis (timing): Koch CG, Li L, Hixson E, Tang A, Gordon S, Longworth D, Phillips S, Blackstone E, Henderson JM. Is it time to refine? An exploration and simulation of optimal antibiotic timing in general surgery. J Am Coll Surg. 2013 Oct;217(4):628-35.http://www.ncbi.nlm.nih.gov/pubmed/23849901

[iv] Surgical antibiotic prophylaxis (tourniquet): Bratzler DW, Houck PM; Surgical Infection Prevention Guidelines Writers Workgroup; American Academy of Orthopaedic Surgeons; American Association of Critical Care Nurses; American Association of Nurse Anesthetists; American College of Surgeons; American College of Osteopathic Surgeons; American Geriatrics Society; American Society of Anesthesiologists; American Society of Colon and Rectal Surgeons; American Society of Health-System Pharmacists; American Society of PeriAnesthesia Nurses; Ascension Health; Association of periOperative Registered Nurses; Association for Professionals in Infection Control and Epidemiology; Infectious Diseases Society of America; Medical Letter; Premier; Society for Healthcare Epidemiology of America; Society of Thoracic Surgeons; Surgical Infection Society. Antimicrobial prophylaxis for surgery: an advisory statement from the National Surgical Infection Prevention Project. Clin Infect Dis. 2004 Jun 15;38(12):1706-15. http://www.ncbi.nlm.nih.gov/pubmed/15227616

[v] Surgical antibiotic prophylaxis (glycaemic control): Berríos-Torres SI, Umscheid CA, Bratzler DW, Leas B, Stone EC, Kelz RR, Reinke CE, Morgan S, Solomkin JS, Mazuski JE, Dellinger EP, Itani KMF, Berbari EF, Segreti J, Parvizi J, Blanchard J, Allen G, Kluytmans JAJW, Donlan R, Schecter WP; Healthcare Infection Control Practices Advisory Committee. Centers for Disease Control and Prevention Guideline for the Prevention of Surgical Site Infection, 2017. JAMA Surg. 2017 Aug 1;152(8):784-791. https://www.ncbi.nlm.nih.gov/pubmed/28467526

[vi] Surgical antibiotic prophylaxis (normothermia): Berríos-Torres SI, Umscheid CA, Bratzler DW, Leas B, Stone EC, Kelz RR, Reinke CE, Morgan S, Solomkin JS, Mazuski JE, Dellinger EP, Itani KMF, Berbari EF, Segreti J, Parvizi J, Blanchard J, Allen G, Kluytmans JAJW, Donlan R, Schecter WP; Healthcare Infection Control Practices Advisory Committee. Centers for Disease Control and Prevention Guideline for the Prevention of Surgical Site Infection, 2017. JAMA Surg. 2017 Aug 1;152(8):784-791. https://www.ncbi.nlm.nih.gov/pubmed/28467526

[vii] Surgical antibiotic prophylaxis (washing): Berríos-Torres SI, Umscheid CA, Bratzler DW, Leas B, Stone EC, Kelz RR, Reinke CE, Morgan S, Solomkin JS, Mazuski JE, Dellinger EP, Itani KMF, Berbari EF, Segreti J, Parvizi J, Blanchard J, Allen G, Kluytmans JAJW, Donlan R, Schecter WP; Healthcare Infection Control Practices Advisory Committee. Centers for Disease Control and Prevention Guideline for the Prevention of Surgical Site Infection, 2017. JAMA Surg. 2017 Aug 1;152(8):784-791. https://www.ncbi.nlm.nih.gov/pubmed/28467526

[viii] Preoperative hair removal: Tanner J, Norrie P, Melen K. Preoperative hair removal to reduce surgical site infection. Cochrane Database Syst Rev. 2011 Nov 9;(11):CD004122. https://www.ncbi.nlm.nih.gov/pubmed/22071812

[ix] Cefaxolin (dose): Berríos-Torres SI, Umscheid CA, Bratzler DW, Leas B, Stone EC, Kelz RR, Reinke CE, Morgan S, Solomkin JS, Mazuski JE, Dellinger EP, Itani KMF, Berbari EF, Segreti J, Parvizi J, Blanchard J, Allen G, Kluytmans JAJW, Donlan R, Schecter WP; Healthcare Infection Control Practices Advisory Committee. Centers for Disease Control and Prevention Guideline for the Prevention of Surgical Site Infection, 2017. JAMA Surg. 2017 Aug 1;152(8):784-791. https://www.ncbi.nlm.nih.gov/pubmed/28467526

Cefaxolin (dose): Bratzler DW, Dellinger EP, Olsen KM, Perl TM, Auwaerter PG, Bolon MK, Fish DN, Napolitano LM, Sawyer RG, Slain D, Steinberg JP, Weinstein RA; American Society of Health-System Pharmacists; Infectious Disease Society of America; Surgical Infection Society; Society for Healthcare Epidemiology of America. Clinical practice guidelines for antimicrobial prophylaxis in surgery. Am J Health Syst Pharm. 2013 Feb 1;70(3):195-283. https://www.ncbi.nlm.nih.gov/pubmed/23327981

[x] Cefaxolin (dose) – pregnant women: Swank ML, Wing DA, Nicolau DP, McNulty JA. Increased 3-gram cefazolin dosing for cesarean delivery prophylaxis in obese women. Am J Obstet Gynecol. 2015 Sep;213(3):415.e1-8. https://www.ncbi.nlm.nih.gov/pubmed/26003059

Cefaxolin (dose) – pregnant women: Elkomy MH, Sultan P, Drover DR, Epshtein E, Galinkin JL, Carvalho B.

Pharmacokinetics of prophylactic cefazolin in parturients undergoing cesarean delivery. Antimicrob Agents Chemother. 2014 Jun;58(6):3504-13. https://www.ncbi.nlm.nih.gov/pubmed/24733461

[xi] Surgical antibiotic prophylaxis (single dose): McDonald M, Grabsch E, Marshall C, Forbes A. Single- versus multiple-dose antimicrobial prophylaxis for major surgery: a systematic review. Aust N Z J Surg. 1998 Jun;68(6):388-96.http://www.ncbi.nlm.nih.gov/pubmed/9623456

Surgical antibiotic prophylaxis (single dose): Bratzler DW, Dellinger EP, Olsen KM, Perl TM, Auwaerter PG, Bolon MK, Fish DN, Napolitano LM, Sawyer RG, Slain D, Steinberg JP, Weinstein RA; American Society of Health-System Pharmacists; Infectious Disease Society of America; Surgical Infection Society; Society for Healthcare Epidemiology of America. Clinical practice guidelines for antimicrobial prophylaxis in surgery. Am J Health Syst Pharm. 2013 Feb 1;70(3):195-283.http://www.ncbi.nlm.nih.gov/pubmed/23327981

[xii] Surgical antibiotic prophylaxis (blood loss > 1500 mL): Berríos-Torres SI, Umscheid CA, Bratzler DW, Leas B, Stone EC, Kelz RR, Reinke CE, Morgan S, Solomkin JS, Mazuski JE, Dellinger EP, Itani KMF, Berbari EF, Segreti J, Parvizi J, Blanchard J, Allen G, Kluytmans JAJW, Donlan R, Schecter WP; Healthcare Infection Control Practices Advisory Committee. Centers for Disease Control and Prevention Guideline for the Prevention of Surgical Site Infection, 2017. JAMA Surg. 2017 Aug 1;152(8):784-791. https://www.ncbi.nlm.nih.gov/pubmed/28467526

[xiii] Surgical antibiotic prophylaxis (re-dosing):Ohge H, Takesue Y, Yokoyama T, Murakami Y, Hiyama E, Yokoyama Y, Kanehiro T, Itaha H, Matsuura Y. An additional dose of cefazolin for intraoperative prophylaxis. Surg Today. 1999;29(12):1233-6.http://www.ncbi.nlm.nih.gov/pubmed/16039702

Surgical antibiotic prophylaxis (re-dosing): National Institute for Health and Care Excellence. Surgical site infections: prevention and treatment clincal guideline, 22 October 2008. https://www.nice.org.uk/guidance/cg74

[xiv] Azithromycin, IV (with cefazolin, IV for emergency caesarean delivery): Tita ATN, Boggess K, Saade G. Adjunctive Azithromycin Prophylaxis for Cesarean Delivery. N Engl J Med. 2017 Jan 12;376(2):182. https://www.ncbi.nlm.nih.gov/pubmed/28076707

Azithromycin, IV (with cefazolin, IV for emergency caesarean delivery): Farmer N, Hodgetts-Morton V, Morris RK. Are prophylactic adjunctive macrolides efficacious against caesarean section surgical site infection: A systematic review and meta-analysis. Eur J Obstet Gynecol Reprod Biol. 2020 Jan;244:163-171. https://www.ncbi.nlm.nih.gov/pubmed/31810022

[xv] Clindamycin: Bratzler DW, Dellinger EP, Olsen KM, Perl TM, Auwaerter PG, Bolon MK, Fish DN, Napolitano LM, Sawyer RG, Slain D, Steinberg JP, Weinstein RA; American Society of Health-System Pharmacists; Infectious Disease Society of America; Surgical Infection Society; Society for Healthcare Epidemiology of America. Clinical practice guidelines for antimicrobial prophylaxis in surgery. Am J Health Syst Pharm. 2013 Feb 1;70(3):195-283. http://www.ncbi.nlm.nih.gov/pubmed/23327981

[xvi] Immunisation –splenectomy (timing): Shatz DV, Schinsky MF, Pais LB, Romero-Steiner S, Kirton OC, Carlone GM. Immune responses of splenectomized trauma patients to the 23-valent pneumococcal polysaccharide vaccine at 1 versus 7 versus 14 days after splenectomy. J Trauma.
1998 May;44(5):760-5; discussion 765-6. http://www.ncbi.nlm.nih.gov/pubmed/9603075

Immunisation –splenectomy (timing):Konradsen HB, Rasmussen C, Ejstrud P, Hansen JB. Antibody levels against Streptococcus pneumoniae and Haemophilus influenzae type b in a population of splenectomized individuals with varying vaccination status. Epidemiol Infect. 1997 Oct;119(2):167-74. http://www.ncbi.nlm.nih.gov/pubmed/9363015

[xvii] Polyvalent pneumococcal vaccine revaccination – splenectomy: Rutherford EJ, Livengood J, Higginbotham M, Miles WS, Koestner J, Edwards KM, Sharp KW, Morris JA Jr. Efficacy and safety of pneumococcal revaccination after splenectomy for trauma. J Trauma. 1995 Sep;39(3):448-52. http://www.ncbi.nlm.nih.gov/pubmed/7473907

Polyvalent pneumococcal vaccine revaccination – splenectomy (dosing schedule): ACIP Practice Guidelines - CDC. Morbidity and Mortality Weekly Report, October 12, 2012, Vol 61, No 40. http://www.cdc.gov/mmwr/preview/mmwrhtml/mm6140a4.htm?s_cid=mm6140a4_w

[xviii] Vaccines – splenectomy: Davies JM, Lewis MP, Wimperis J, Rafi I, Ladhani S, Bolton-Maggs PH; British Committee for Standards in Haematology. Review of guidelines for the prevention and treatment of infection in patients with an absent or dysfunctional spleen: prepared on behalf of the British Committee for Standards in Haematology by a working party of the Haemato-Oncology task force. Br J Haematol. 2011 Nov;155(3):308-17. http://www.ncbi.nlm.nih.gov/pubmed/21988145

Vaccines – splenectomy: Rubin LG, Levin MJ, Ljungman P, Davies EG, Avery R, Tomblyn M, Bousvaros A, Dhanireddy S, Sung L, Keyserling H, Kang I, Infectious Diseases Society of America. 2013 IDSA clinical practice guideline for vaccination of the immunocompromised host. Clin Infect Dis. 2014 Feb;58(3):e44-100. http://www.ncbi.nlm.nih.gov/pubmed/24311479

Vaccines – splenectomy: Davidson RN, Wall RA. Prevention and management of infections in patients without a spleen. ClinMicrobiol Infect. 2001 Dec;7(12):657-60. http://www.ncbi.nlm.nih.gov/pubmed/11843905

Vaccines – splenectomy:Bisharat N, Omari H, Lavi I, Raz R. Risk of infection and death among post-splenectomy patients. J Infect. 2001 Oct;43(3):182-6. http://www.ncbi.nlm.nih.gov/pubmed/11798256

CHAPTER 12
ANAESTHESIOLOGY AND INTENSIVE CARE

Anaesthetic and sedative medication may only be administered by medical practitioners trained and experienced in their use.

Sound theoretical and practical training followed by several years of supervised experience in the administration of anaesthetics is essential to develop the skills of the anaesthetist. Even within the recommended dosage range, anaesthetic agents can cause death when inappropriately used and only as a last resort should they be administered by non-specialised personnel. *LoE:III*[i]

Medicines and equipment for resuscitation should be functional and immediately available whenever general anaesthesia, regional anaesthesia or sedation is administered.

The following is a list of medicines required for anaesthesia that should be available at district and regional hospitals.

The doses of the medicines given are those recommended for healthy adults. Patients who are acutely or chronically sick, and or elderly, may require substantial reductions in the doses given otherwise life-threatening adverse effects may ensue.

12.1 PREMEDICATION

- Lorazepam, 1–2 mg, oral, the night before surgery and 1–2 hours preoperatively
  - Use half the dose in the elderly.
  - Duration of action (10–20 hours).
  - Unsuitable for day case surgery.

  LoE:III[ii]
- Midazolam, 5–7.5 mg, oral, one hour preoperatively.
  - **Use only in healthy adults <65 years of age.**
  - Duration of action 1–4 hours.
  - Suitable for day case surgery. *LoE:III*[iii]

12.2 ANAESTHESIA, GENERAL

12.2.1 INTRAVENOUS INDUCTION (AND/OR MAINTENANCE) AGENTS

Inject intravenous induction agents over 30 seconds (>60 seconds in the elderly).
Titrate the dose to effect.

Respiratory depression occurs following induction of anaesthesia and ventilation should be supported as required.
Administer at appropriate doses, after consideration of patient factors, surgical factors and contraindications:

» Propofol is the most widely used IV induction agent but can produce hypotension.
» Etomidate or ketamine is preferred in haemodynamically unstable patients.
» Thiopental has a rapid onset, is contraindicated in porphyria and may be preferred for Caesarean deliveries. *LoE:III[iv]*

- Propofol, IV, 1.5–2.5 mg/kg.
  - 6–12 mg/kg/hour IV infusion for maintenance, if volatile agent use contraindicated.
- Etomidate, IV, 0.3 mg/kg (0.2–0.6 mg/kg)
- Ketamine, IV, 1–2 mg/kg.
- Thiopental, IV, 3–5 mg/kg.

12.2.2 INHALATION AGENTS

12.2.2.1 INDUCTION

In adults, intravenous induction is preferable.
Inhalational induction is reserved for patients with difficult airways or severe needle phobia.
Use only halothane or sevoflurane (isoflurane is too irritant). Halothane can cause hepatitis after repeated exposure within 3 months. Halothane sensitises the heart to catecholamines and may cause cardiac dysrhythmias, particularly if anaesthesia is too light or the patient hypercarbic.
Sevoflurane is not associated with these problems, has a faster onset and emergence time.

- Halothane, titrated to effect.

OR

- Sevoflurane, titrated to effect. *LoE:III[iv]*

12.2.2.2 MAINTENANCE

In spontaneously breathing patients, the dose of a volatile agent is titrated to clinical effect. If a neuromuscular blocking agent has been used, the dose of the volatile agents must be adequate to prevent awareness. This is about 1 minimum alveolar concentration (MAC), but must be titrated according to clinical signs of awareness (e.g. tachycardia, hypertension, sweating, lacrimation).

- Isoflurane (MAC = 1.2%).

12.3 MUSCLE RELAXANTS

Used to facilitate intubation and to provide intraoperative muscle relaxation for surgery. It must not be used if difficult intubation anticipated.

12.3.1 DEPOLARISING MUSCLE RELAXANTS

- Suxamethonium, IV, 1–1.5 mg/kg.
  - Onset 30–60 seconds.
  - Duration 5 minutes.
  - Repeated doses associated with bradycardia and prolonged neuromuscular block.
  - Contraindicated in patients at risk for developing suxamethonium-induced hyperkalaemia, e.g. upper or lower motor neuron defect, prolonged chemical denervation (ICU >3 days), direct muscle trauma, tumour or inflammation, burns, disuse atrophy, severe infection, pre-existing hyperkalaemia.

LoE:III[vi]

12.3.2 NON-DEPOLARISING MUSCLE RELAXANTS (NDMR)

Use a nerve stimulator to monitor effect and determine when subsequent doses (about a fifth of the intubating dose) are required.

Higher doses result in shorter onset times but longer duration of action.

- Intermediate-acting neuromuscular blocking agents, e.g.:
- Cisatracurium (shorter-acting) *LoE:III*[vii]
  - Intubation dose 0.1–0.15 mg/kg.
  - Onset 3–5 minutes.
  - Duration of action 45–55 minutes.
  - Eliminated by Hoffman degradation, therefore can be used in renal or liver impairment.
- Vecuronium
  - Intubation dose 0.08–0.1 mg/kg.
  - Intubate after 2 minutes. *LoE:III*[viii]
  - Duration 20–30 minutes.
  - Eliminated by liver and kidney: avoid in renal and liver impairment.

12.3.3 MUSCLE RELAXATION FOR RAPID SEQUENCE INTUBATION

Patients at risk of aspiration (e.g. emergency surgery, incomplete gastric emptying) require a rapid sequence intubation.
An IV induction agent is given through an IV line with fast running fluids, immediately followed by a rapidly acting muscle relaxant.
Cricoid pressure is applied and then intubation proceeds.
The rapid onset of action enables the time to intubation to be short enough to avoid mask ventilation, as this can result in gastric insufflation and aspiration of gastric contents.

- Suxamethonium, 1–1.5 mg/kg, IV. (See section 12.3.1: Depolarising muscle relaxants).
  - Preferred agent as, in the event of a failed intubation, it wears off quickly enabling spontaneous respiration to resume.
  - Contraindications to suxamethonium
    - Congenital and acquired medical conditions associated with severe, potentially lethal suxamethonium-induced hyperkalaemia.
    - Malignant hyperthermia. *LoE:I*[ix]

If suxamethonium is contra-indicated, consider:

- Rocuronium, 0.9 mg/kg, IV.
  - Duration +/- 60 minutes. *LoE:III*[x]

Sub-optimal conditions for intubating and prolonged effect can be problematic in the event of a difficult or failed intubation and if the procedure is short.

12.3.4 MEDICINES TO REVERSE MUSCLE RELAXATION

Only administer when the clinical signs of NDMR are wearing off or at least 2 twitches occur using train-of-four on nerve stimulator.

Neostigmine has profound cholinergic effects and, to counteract resultant profound bradycardia, is administered mixed with an anticholinergic agent, atropine or glycopyrrolate.

Whilst atropine is effective and can be used for this purpose in otherwise healthy patients, the onset of neostigmine and duration of action more closely matches that of glycopyrrolate, so this is the preferred combination agent for patients who poorly tolerate tachycardia or bradycardia.

- Neostigmine, IV, 50 mcg/kg.

LoE:III[xi]

WITH EITHER:

- Atropine, IV, 20 mcg/kg (maximum 1.2 mg).

LoE:III[xii]

OR

Glycopyrrolate, IV, 10 mcg/kg.

LoE:III[xiii]

12.4 PERIOPERATIVE ANALGESIA

R52.9

» The perioperative period includes the preoperative, intraoperative and post-operative stages of surgery.
» Perioperative analgesia should be multi-modal, i.e. use analgesics, where possible, from different classes to reduce side effects from high doses of a single agent (e.g. paracetamol, NSAID and a weak/strong opioid) with either a regional block or wound infiltration with local anaesthetic.
» Patients with pain before surgery should be given analgesia preoperatively.
» Paracetamol may be given orally with premedication to prophylactically reduce perioperative pain.
» Intraoperatively, analgesics are given intravenously and/or a central neuraxial or regional local anaesthetic block may be used. The analgesic effect of these may extend into the early postoperative period.
» Postoperatively analgesics are given IV, IM and/or rectally, until the patient is able to take oral medication. Patients with a functioning block may not require analgesia until the block wears off but analgesics should be prescribed in anticipation of this.
» Pain severity should be assessed frequently post-operatively (see Section 12.5.3: Postoperative analgesia ward prescriptions).

12.4.1 PERIOPERATIVE ANALGESICS

12.4.1.1 ORAL ANALGESICS

- Paracetamol, oral, 500 mg to 1 g, 4 to 6 hourly as required (to a maximum of 4 g in 24 hours).
  - Maximum dose: 15 mg/kg/dose.

AND

LoE:I[xiv]

- Tramadol, oral, 50 to 100 mg, 6 hourly as a starting dose. (Doctor prescribed.)
  - May be increased to a maximum daily dose of 400 mg.
  - Avoid in head injury and epilepsy.
  - Improved effect when given with paracetamol.

AND

LoE:III[xv]

- NSAID, e.g.:
- Ibuprofen, oral, 400 mg 8 hourly with meals.

Note: Do not administer NSAIDs to patients at risk of hypovolaemia, renal impairment or gastrointestinal bleeding. Avoid in patients with asthma who

experience bronchospasm with NSAIDs. LoE:III[xvi]

12.4.1.2 INTRAVENOUS ANALGESICS

- Fentanyl, IV, 1–2 mcg/kg
  - Onset ± 3 minutes, duration of action 30–60 minutes. Higher doses last longer. LoE:III[xvii]

- Morphine, IV/IM, 3–5 mg as a single dose then further boluses at intervals of 5–10 minutes and monitor all vitals closely. LoE:III[xviii]
  - Dilute 10 mg up to 10 mL with sodium chloride 0.9%.
  - Total maximum dose: 10 mg.
  - Repeat after 4 hours if necessary.
  - Monitor response to pain and effects on respiration and BP.
  - Onset 5-10 minutes. Duration of action ± 3 hours.
  - Histamine release may cause intraoperative hypotension.

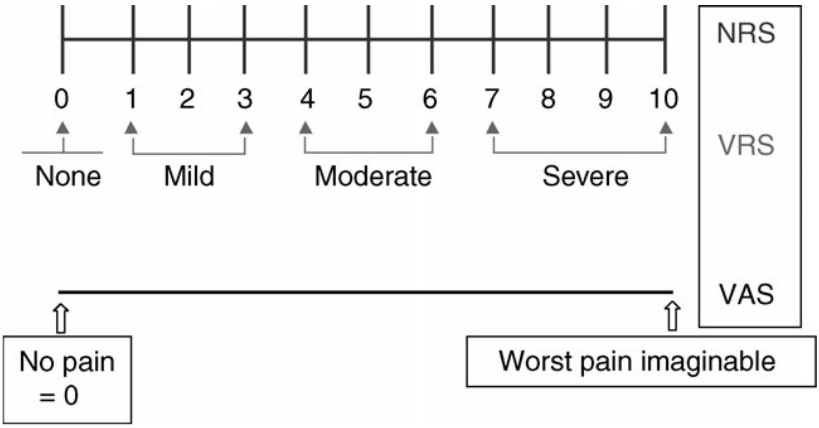
- Ketamine, IV, 0.1–0.3 mg/kg – a subanaesthetic dose given pre-incision may reduce persistent post-surgical pain. LoE:I[xix]

12.4.2 POSTOPERATIVE PAIN IN THE RECOVERY ROOM

R52.0

Pain should be assessed on arrival in the recovery room and at regular intervals postoperatively. Pain Scores should be recorded with other routine postoperative observations.

A Numeric Rating Scale (NRS) can be used to score pain:



Source: Breivik H, Borchgrevink PC, Allen SM, Rosseland LA, Romundstad L, Hals EK, Kvarstein G, Stubhaug A. Assessment of pain. *Br J Anaesth.* 2008 Jul;101(1):17-24.

The patient is asked to indicate on the scale the numeric value that best indicates their pain intensity or verbally if they cannot visualise the scale.

Severe pain (use lower doses if pain less):

- Morphine, IV, to a total maximum dose of 10 mg (See Appendix II, for individual dosing and monitoring for response and toxicity).
    - Monitor conscious level and pulse oximetry continuously. Also monitor respiration, heart rate and BP at 5 minute intervals and for at least 20 minutes after the last IV morphine bolus.

In patients at high risk for respiratory depression, tramadol may be used instead of morphine as it causes less respiratory depression (although respiratory depression may still occur with tramadol).

Tramadol is a weak opioid agonist and increases spinal cord levels of serotonin and noradrenaline.

- Tramadol, IV, 50–100 mg over 3 minutes to reduce side-effects of nausea and vomiting (Specialist prescribed).
    - Ceiling effect i.e. higher doses do not improve pain relief. *LoE:III*[xx]

In addition to morphine or tramadol, diclofenac may also be given to supplement analgesia and reduce opioid requirements:

- Diclofenac, **deep IM**, 75 mg 12 hourly.
    - Administer for a maximum of 2 days.
    - Avoid the same injection site.
    - Counsel patient prior to injection of adverse events (scarring) at inject site, if applicable. *LoE:III*[xxi]

12.4.3 POSTOPERATIVE ANALGESIA WARD PRESCRIPTIONS

Analgesia should be prescribed according to the severity of pain anticipated from the surgery and the anticipated, appropriate, postoperative route of administration.

Pain should be assessed at regular intervals on the ward postoperatively. Pain scores should be recorded with other routine postoperative observations.

Respiratory rate should be monitored for opioid-induced respiratory depression.

12.4.3.1 EXAMPLES OF WARD PRESCRIPTIONS FOR POSTOPERATIVE ANALGESIA ACCORDING TO ANTICIPATED PAIN SEVERITY

R52.9

MILD PAIN:

- Paracetamol, oral, 500 mg to 1 g, 4 to 6 hourly as required (to a maximum of 4 g in 24 hours).
  - Maximum dose: 15 mg/kg/dose.

AND

- NSAID, oral, e.g.:
- Ibuprofen, oral, 400 mg 8 hourly after meals.

CAUTION

Concomitant use of more than one oral NSAID has no additional clinical benefit and only increases toxicity.

Use of all NSAIDs is associated with increased risks of gastrointestinal bleeding, renal dysfunction, and cardiovascular events (stroke and myocardial infarction).

NSAIDs should be used judiciously at the lowest effective dose for the shortest duration. Explore and manage exacerbating factors for pain. See section 26.1: Chronic pain.

Do not use NSAID in pregnancy or while breastfeeding.

AND

- Tramadol, oral, 50 to 100 mg, 6 hourly as a starting dose. (Doctor prescribed.)
  - May be increased to a maximum daily dose of 400 mg.
  - Avoid in head injury and epilepsy.
  - Improved effect when given with paracetamol.

MODERATE PAIN:

- Paracetamol, oral, 500 mg to 1 g, 4 to 6 hourly as required (to a maximum of 4 g in 24 hours).
  - Maximum dose: 15 mg/kg/dose.

AND

- NSAID, oral, e.g.:
- Ibuprofen, oral, 400 mg 8 hourly with meals.

CAUTION
Concomitant use of more than one oral NSAID has no additional clinical benefit and only increases toxicity.
Use of all NSAIDs is associated with increased risks of gastrointestinal bleeding, renal dysfunction, and cardiovascular events (stroke and myocardial infarction).
NSAIDs should be used judiciously at the lowest effective dose for the shortest duration. Explore and manage exacerbating factors for pain. See section 26.1: Chronic pain.
Do not use NSAID in pregnancy or while breastfeeding.

AND

- Tramadol, oral, 50 to 100 mg, 6 hourly as a starting dose. (Doctor prescribed.)
  - May be increased to a maximum daily dose of 400 mg.
  - Avoid in head injury and epilepsy.
  - Improved effect when given with paracetamol.

OR

Morphine, IM, 0.1–0.2 mg/kg 4 hourly or IV via a patientcontrolled analgesia device (see below).

SEVERE PAIN:

- Morphine, IM, 0.1–0.2 mg/kg 4 hourly or IV via a PCA device.

AND

- Paracetamol, oral, 500 mg to 1 g, 4 to 6 hourly as required (to a maximum of 4 g in 24 hours).
  - Maximum dose: 15 mg/kg/dose.

AND

- NSAID, e.g.:
- Ibuprofen, oral, 400 mg 8 hourly with meals.

LoE:III[pxxii]

Note:

Patient controlled analgesia

If a device is available that will administer patient controlled analgesia:

- Morphine, IV, in boluses of 1 mg every 6-10 minutes, with a maximum dose of 0.1–0.2 mg/kg 4 hourly.
  - In the elderly and frail, the dose of morphine should be reduced and the dosage interval increased.

LoE:I[pxxiii]

If unable to take oral medication, stop oral ibuprofen and use:

- Diclofenac, **deep IM**, 75 mg 12 hourly, to upper, outer quadrant of buttock.
  - Administer for a maximum of 2 days.
  - Avoid the same injection site.

- Counsel patient prior to injection of adverse events (scarring) at injection site if applicable.

LoE:III[xxiv]	

12.5 INTRAVENOUS FLUIDS

The following IV fluids should be available for perioperative fluid replacement and maintenance therapy.

12.5.1 CRYSTALLOIDS

Most commonly used crystalloid for perioperative fluid maintenance:

- Sodium chloride 0.9%, IV.

Higher sodium content than indicated if there is a perioperative risk of hyponatraemia e.g. transurethral resection of prostate.
Balanced solutions may be appropriate in some patients (i.e. presentation with hyponatraemia, previous renal placement therapy):

- Balanced solution, e.g.:
- Ringer Lactate, IV.

LoE:I[xxv]

12.6 MEDICINES TO TREAT COMPLICATIONS OF ANAESTHESIA

12.6.1 MALIGNANT HYPERTHERMIA

T88.3

- Dantrolene IV, 2.5 mg/kg as a single dose (preferably through large bore cannula).
  - Reconstitute with 60 mL water for injection. For a 70 kg patient, 175 mg (9 vials) is required.
  - Administer subsequent doses to clinical effect (cardiac and respiratory symptoms stabilise, muscle tone and body temperature reduced).
  - Doses higher than 10 mg/kg is uncommon and the clinician should question the diagnosis.
  - Although, high doses of 10 mg/kg may be required in muscular males.

LoE:III[xxvi]

12.6.2 LOCAL ANAESTHETIC TOXICITY

T41.3

Airway management:

- Ventilate with 100% oxygen.

Seizure suppression:

- Diazepam, IV, 10 mg.

Cardiopulmonary resuscitation may be required:

- Reduce individual adrenaline (epinephrine) doses to <1 mcg/kg.

LoE:III[xxvii]

- Lipid emulsion (20%), IV, 1.5 mL/kg over 1 minute, then continuous infusion 0.25 mL/kg/minute.
  - Repeat bolus 1–2 times for persistent cardiovascular collapse.
  - Double infusion rate to 0.5 mL/kg/minute if BP remains low.
  - Continue infusion for at least 10 minutes after cardiovascular stability attained.
  - Recommended upper limit: approximately 10 mL/kg lipid emulsion over the first 30 minutes.

LoE:III[xxviii]

12.6.3 ANAESTHETIC-RELATED ACUTE HYPOTENSION

I95.81

Treat the cause of hypotension.
Ensure appropriate fluids are given to correct hypovolaemia.
The medicines given below all require significant dilution before administration.

- Adrenergic and dopaminergic agents, e.g.:
- Ephedrine IV, 3–5 mg as a single dose and then further boluses as required to a maximum of 30 mg.
  - Increases heart rate and contractility, and vasoconstrictor.
  - Repeated administration can result in tolerance and tachyphylaxis.
  - Alternative vasopressor infusion (e.g. adrenaline (epinephrine)) may be needed to mitigate unresponsiveness to treatment.

LoE:III[xxix]

OR

Phenylephrine IV, 50–100 mcg as a single dose and then infuse at 60–180 mcg/minute.

- Vasoconstrictor. *LoE:III*[xxx]
- High doses may cause significant reflex bradycardia: treat this by discontinuing the phenylephrine only.

12.6.4 ANAESTHETIC-RELATED ACUTE HYPERTENSION

I97.3

To obtund the hypertensive response to intubation e.g. pre-eclampsia:

- Alfentanil, IV, 7.5 mcg/kg (with magnesium sulfate, IV 30 mg/kg).

LoE:III

During anaesthesia or post-operatively, establish the cause (e.g. light anaesthesia or inadequate pain relief) and treat as appropriate.

- Labetalol IV, 5–10mg IV over 2 minutes.
  - Repeated at intervals of at least 5 minutes to maximum 200 mg.

- Duration of action 50 minutes.
- Vasodilates and slows heart rate. *LoE:III*[xxxi]

12.6.5 POSTOPERATIVE NAUSEA AND VOMITING (PONV)

12.6.5.1 PREVENTION OF PONV

R11.2

Patients identified preoperatively as medium or high risk for PONV should be considered for prophylactic antiemetics.
Prophylactic antiemetics also required if postoperative vomiting is potentially dangerous, e.g. after jaws wired, open eye surgery, oesophageal surgery.
High risk patients should receive anti-emetics from ≥ 1 class.
Adequate IV hydration associated with less PONV.

Risk factors for PONV	**Points**
Female Gender	1
Non-Smoker	1
History of PONV and/or motion sickness	1
Postoperative opioids	1
Sum	0–4

Points	**Risk for PONV (%)**	**Risk category**
0	10	Low
1	20	Low
2	40	Medium
3	60	High
4	80	High

Class	**Anti-emetic**	**Prophylactic Dose and timing**	**Notes**
Corticosteroid (glucorticoids)	e.g.: Dexamethasone	4-8 mg, IV, on induction. *LoE:II*[xxxii]	Increases blood glucose in diabetics. Only used for prophylaxis, not established PONV.
5-HT_3 receptor antagonist	e.g.: Ondansetron	4–8 mg, slow IV/IM, on induction. *LoE:III*[xxxiii]	Prolongs QTc interval
Phenothiazine	Promethazine	6.25–12.5 mg, IV (large bore cannula) diluted to 20 mL over 10-20 minutes, or	Intra-arterial injection causes gangrene. Extravasation or subcutaneous injection

		deep IM, at end of surgery.	associated with skin necrosis. Anticholinergic side effects and sedation.

12.6.5.2 TREATMENT OF PONV

R11.2

Ensure adequate hydration and correct hypotension if present.
Give an emetic from a different class than the prophylactic agent given (except dexamethasone, which is only used for prophylaxis).

- Metoclopramide, IM/IV
  - If <60 kg: 5 mg IM or IV (over 2 minutes).
  - If ≥60 kg: 10 mg IM or IV (over 2 minutes).
  - Repeat 8 hourly if required.

Note: Metoclopramide can cause extrapyramidal side effects.

Treat acute dystonic reactions with:

- Anticholinergic agent, e.g.:
- Biperiden, IM/IV, 2 mg.
  - Repeat as necessary.

If an anticholinergic agent is not available:

- Promethazine, deep IM, 25–50 mg.
  - In the elderly 25 mg.

If an anticholinergic agent or promethazine is not available:

- Diazepam, IV, 5–10 mg for symptom relief. *LoE:III*

12.6.6 ACID ASPIRATION PROPHYLAXIS

O74.0

The use of a non-particulate, non-effervescent antacid reduces the risk of pneumonitis if gastric fluid is aspirated. Give to patients at risk of aspiration, e.g. pregnant women before Caesarean delivery.

- Sodium citrate, 0.3M, oral, 30 mL.
  - Not more than 30 minutes pre-induction of anaesthesia.

LoE:[xxxiv]

12.7 ANAESTHESIA, SPINAL (INTRATHECAL)

Only preservative free medicines may be used.
Larger doses cause block to spread higher, with risks of respiratory depression, hypotension and loss of consciousness.

- Bupivacaine 0.5% (Spinal use)
  - Give up to 3 mL according to desired level of block.

- Becomes hypobaric (light) within CSF so block may spread higher than anticipated.

- Bupivacaine 0.5% with dextrose (Spinal use)
  - Give up to 3 mL according to desired level of block.
  - Hyperbaric (heavy) so block spreads according to patient position.

To increase duration of analgesia:
ADD
- Fentanyl, 10–25 mcg (i.e. small amounts).

Caesarean deliveries
Lower doses are required due to physiologic changes of pregnancy:
- Bupivacaine 0,5% with dextrose, 1.8 mL (9 mg).

AND
- Fentanyl, 10 mcg (0.2 mL).

12.7.1 ANTICOAGULANTS AND SPINAL OR EPIDURAL BLOCKS

Patients on anticoagulants are at risk of developing a spinal haematoma with subsequent paralysis after a spinal or epidural block. These anticoagulants should be stopped before the spinal or epidural is performed according to the guidelines given below. In order to encourage safe and quality care of patients, **please consult a specialist prior to attempting blocks on patients on anticoagulants**. There are a range of oral anticoagulation, with each having specific recommendations with regard to neuraxial blocks.

Timing of anticoagulants in patients receiving neuraxial anaesthesia:

Anticoagulant	Before Neuraxial Block	After Neuraxial block
Warfarin, oral	Consult with specialist to stop warfarin.	Restart after neuraxial block performed (do not delay) and epidural catheter removed. Monitor INR daily with indwelling catheter.
Unfractionated Heparin, SC	Neuraxial techniques may be performed if total daily dose is <10 000U. Check PTT if higher doses are used.	
Unfractionated Heparin, IV	Stop heparin 4-6 hours and check PTT<40	Wait 1 hour before next bolus/infusion restarted.
Prophylactic LMWH, SC	12 hours after last dose	4 hours after neuraxial block performed and epidural catheter removed

Therapeutic LMWH, SC	24 hours after last dose	>24 hours *and* consult a specialist (bleeding risk of surgery should be assessed).

LoE:II[xxxv]

Note. After neuraxial block or epidural catheter removal, patients should be observed closely for new or progressive neurological symptoms. A spinal haematoma can result in permanent paralysis unless decompressive surgery is performed within 8 hours of paralysis onset.

Clopidogrel and platelet GPIIb/IIIa inhibitors have variable durations of effects on clotting after stopping these medications. Specialist advice should be sought before performing neuraxial blocks on patients receiving these medications.

For patients on warfarin the use of bridging anticoagulation (giving heparin after warfarin is stopped in preparation for surgery or invasive procedures) remains unsettled. Practitioners should exercise careful judgment of competing risks in individual patients. Heparin may increase the risk of bleeding. Whatever practice is adopted the most important consideration is to ensure that adequate anticoagulation with warfarin is re-instituted once the risk of bleeding is past.

12.8 ANAESTHESIA, EPIDURAL

Only preservative free medicines may be used.
Local anaesthetics are administered through a catheter inserted into the epidural space at a spinal level appropriate for the surgery.
Aspiration and a test dose (2–3 mL) of local anaesthetic should be given to confirm catheter not intravascular or intrathecal. Subsequent doses should be fractionated (3–5 mL boluses).

- Bupivacaine 0.5%.
  - Onset ±10 minutes.
  - Duration ±4 hours.
  - Motor block is less with lower concentrations.
  - Maximum dose 2 mg/kg.

LoE:III[xxxvi]

12.9 PERIPHERAL NERVE BLOCK OR WOUND INFILTRATION

Only preservative free medicines may be used for nerve blocks.
Lidocaine has a faster onset of action than bupivacaine, but a shorter duration of action.

- Lidocaine 1% or 2%.

- Higher concentrations cause more pain on injection.
- Maximum dose: 3 mg/kg.

- Lidocaine 2% plus adrenaline.
  - Not to be used in areas supplied by an end-artery e.g. finger, ear, penis.
  - Maximum dose: 7 mg/kg.

- Bupivacaine 0.5%
  - Not be used in mucosal areas as risk of systemic toxicity.
  - Maximum dose: 2 mg/kg.

LoE:III[xxxvii]

12.10 ANAESTHESIA, TOPICAL

- Lidocaine jelly, topical, 2 g/100mL.
  - For urethral catheterisation: female 5–7 mL, male 10–15 mL.

LoE:III[xxxviii]

- Lidocaine topical spray, 4%.
  - Maximum dose 160 mg.
  - To assist with awake intubation or reduce haemodynamic response to intubation.

LoE:III[xxxix]

For venepuncture analgesia in adults or oncology patients requiring repeated invasive procedures (e.g. lumbar punctures, venepuncture):

- Lidocaine/prilocaine, topical cream, 2.5/2.5%.
  - Apply at least 1 hour before and cover with occlusive dressing.

LoE:III[xl]

12.11 SEDATION

See chapter 23: Sedation.

12.12 PAIN, CHRONIC

See chapter 26: Pain.

12.13 INTENSIVE CARE

12.13.1 NUTRITIONAL SUPPORT

E63.9

Establish a multidisciplinary nutrition support team to assess and address the nutritional requirements of patients. This team should include a dietician.

Nutrition support should be considered in patients at risk, defined as those who have a poor absorptive capacity and/or high nutrient losses and/or increased nutritional needs from causes such as catabolism.

Oral feeding, if feasible, is preferred.
Enteral tube feeding is the next best option.
Total parenteral nutrition (TPN) is indicated in exceptional circumstances.
For short-term care (≤ two weeks), the current standard formulas in multi-chamber bags that have a long shelf-life are considered to provide adequate nutritional support. Clinicians should be aware of the possibility of clinically important hypovitaminosis in individual patients, and replace selected vitamins where appropriate.

Refer to the most current version of the National Department of Health Parenteral Nutrition Practice Guidelines for Adults, available at: www.health.gov.za

In selecting the treatment modality, the team should consider:
» The likely duration of nutrition support.
» Patient activity levels and the underlying clinical condition, e.g. catabolism.
» Gastrointestinal tolerance, potential metabolic instability and risks of re-feeding.

Potential complications harms of nutritional support include:
» Re-feeding syndrome: Hypophosphataemia occurs when patients are re-fed too quickly with high carbohydrate feeds. The syndrome usually begins within 4 days of re-feeding. A multitude of life-threatening complications involving multiple organs may occur, causing: respiratory failure, cardiac failure, cardiac dyshythmias, rhabdomyolysis, seizures, coma, red cell and leukocyte dysfunction. The most effective way to prevent re-feeding syndrome is that feeds should be started slowly with aggressive supplementation of magnesium, phosphate and potassium.
» Diarrhoea.
» Lactose intolerance.

Regularly review the need for ongoing therapeutic nutritional support.

Vitamin and mineral supplementation should be considered on a case-by-case basis.

Enteral tube feeding
Enteral tube feeding should be used in patients who cannot swallow or who are at risk of aspiration.
Patients should be fed via a nasogastric tube unless this is contra-indicated.
Patients with upper gastro-intestinal dysfunction (or an inaccessible upper gastro-intestinal tract) should receive post-pyloric (duodenal or jejunal) feeding.
Percutaneous endoscopic gastrostomy feeding should be used in patients likely to need long-term (≥4 weeks) enteral tube feeding.

Parenteral feeding

The team should consider parenteral nutrition in patients who are malnourished or at risk of malnutrition and fit the following criteria:

» inadequate or unsafe oral and enteral tube nutritional intake, or
» a non-functional, inaccessible or perforated (leaking) gastrointestinal tract.

Note: For short-term care, the current standard formulas in multi-chamber bags that have a long shelf-life are considered to provide adequate nutritional support.

The addition of glutamine does not confer any clear clinical benefits and is thus not recommended.

Parenteral nutrition can be withdrawn once adequate oral or enteral nutrition is tolerated and nutritional status is stable. Withdrawal should be planned and done in a stepwise way with a daily review of the patient's progress.

References:

[i] Anaesthetics and sedatives: World Health Organisation. WHO model prescribing information: Drugs used in anaesthesia, 1994. https://apps.who.int/medicinedocs/en/d/Jh2929e/2.html

[ii] Lorazepam, oral: South African Medicines Formulary. 12th Edition. Division of Clinical Pharmacology. University of Cape Town, 2016.

[iii] Midazolam, IV: Walker KJ, Smith AF. Premedication for anxiety in adult day surgery. Cochrane Database Syst Rev. 2009 Oct 7;(4):CD002192. https://www.ncbi.nlm.nih.gov/pubmed/19821294

Midazloma, IV: South African Medicines Formulary. 12th Edition. Division of Clinical Pharmacology. University of Cape Town, 2016.

[iv] Thiopental, IV (contraindication-porphyria): South African Medicines Formulary. 12th Edition. Division of Clinical Pharmacology. University of Cape Town, 2016.

[v] Sevoflurane: National Department of Health, Essential Drugs Programme. Medicine review: Sevoflurane, 5 March 2015. http://health.gov.za/

Sevoflurane: National Department of Health, Essential Drugs Programme. Cost analysis report for halothane versus sevoflurane for induction of anaesthesia in adults at hospital level, 10 September 2015. http://health.gov.za/

[vi] Suxamethonium: South African Medicines Formulary. 12th Edition. Division of Clinical Pharmacology. University of Cape Town, 2016.

[vii] Intermediate-acting neuromuscular blocking agents: South African Medicines Formulary. 12th Edition. Division of Clinical Pharmacology. University of Cape Town, 2016.

Intermediate-acting neuromuscular blocking agents: Joint Formulary Committee. British National Formulary. London: BMJ Group and Pharmaceutical Press; 2019.

[viii] Vecuronium: South African Medicines Formulary. 12th Edition. Division of Clinical Pharmacology. University of Cape Town, 2016.

[ix] Suxamethonium: Perry JJ, Lee JS, Sillberg VA, Wells GA. Rocuronium versus succinylcholine for rapid sequence induction intubation. Cochrane Database Syst Rev. 2008 Apr 16;(2):CD002788. http://www.ncbi.nlm.nih.gov/pubmed/18425883

[x] Rocuronium: Perry JJ, Lee JS, Sillberg VA, Wells GA. Rocuronium versus succinylcholine for rapid sequence induction intubation. Cochrane Database Syst Rev. 2008 Apr 16;(2):CD002788. http://www.ncbi.nlm.nih.gov/pubmed/18425883

Rocuronium: Contract circular price: HP06-2014SVP. http://health.gov.za/

Rocuronium: National Department of Health, Essential Drugs Programme. Medicine review: Rocuronium for muscle relaxation for rapid sequence induction, 31 March 2015. http://health.gov.za/

[xi] Neostigmine: South African Medicines Formulary. 12th Edition. Division of Clinical Pharmacology. University of Cape Town, 2016.

[xii] Atropine: South African Medicines Formulary. 12th Edition. Division of Clinical Pharmacology. University of Cape Town, 2016.

[xiii] Glycopyrrolate: South African Medicines Formulary. 12th Edition. Division of Clinical Pharmacology. University of Cape Town, 2016.

[xiv] Paracetamol, oral: The South African Society of Anaesthesiologists. South African Acute Pain Guidelines. SAJAA 2009;15(6):1-120. http://www.sasaweb.com/content/images/SASA_Pain_Guidelines.pdf

Paracetamol: Bandolier. Oxford league table of analgesics in acute pain. Available at: http://www.medicine.ox.ac.uk/bandolier/booth/painpag/acutrev/analgesics/leagtab.html

[xv] Tramadol, oral: The South African Society of Anaesthesiologists. South African Acute Pain Guidelines. SAJAA 2009;15(6):1-120. http://www.sasaweb.com/content/images/SASA_Pain_Guidelines.pdf

[xvi] Ibuprofen, oral: The South African Society of Anaesthesiologists. South African Acute Pain Guidelines. SAJAA 2009;15(6):1-120. http://www.sasaweb.com/content/images/SASA_Pain_Guidelines.pdf

[xvii] Fentanyl, IV: The South African Society of Anaesthesiologists. South African Acute Pain Guidelines. SAJAA 2009;15(6):1-120. http://www.sasaweb.com/content/images/SASA_Pain_Guidelines.pdf

Fentanyl, IV: Scholz J, Steinfath M, Schulz M. Clinical pharmacokinetics of alfentanil, fentanyl and sufentanil. An update. Clin Pharmacokinet. 1996 Oct;31(4):275-92. http://www.ncbi.nlm.nih.gov/pubmed/8896944

[xviii] Morphine, IV (dosing): South African Medicines Formulary. 12th Edition. Division of Clinical Pharmacology. University of Cape Town, 2016.

[xix] Ketamine, IV: McNicol ED, Schumann R, Haroutounian S. A systematic review and meta-analysis of ketamine for the prevention of persistent post-surgical pain. Acta Anaesthesiol Scand. 2014 Nov;58(10):1199-213. http://www.ncbi.nlm.nih.gov/pubmed/25060512

Ketamine, IV: Brinck EC, Tiippana E, Heesen M, Bell RF, Straube S, Moore RA, Kontinen V. Perioperative intravenous ketamine for acute postoperative pain in adults. Cochrane Database Syst Rev. 2018 Dec 20;12:CD012033. https://www.ncbi.nlm.nih.gov/pubmed/30570761

[xx] Tramadol, IV: Houmes RJ, Voets MA, Verkaaik A, Erdmann W, Lachmann B. Efficacy and safety of tramadol versus morphine for moderate and severe postoperative pain with special regard to respiratory depression. Anesth Analg. 1992 Apr;74(4):510-4. http://www.ncbi.nlm.nih.gov/pubmed/1554117

Tramadol, IV: National Department of Health, Essential Drugs Programme. Medicine review: Tramadolol, IV July 2015. http://health.gov.za/

[xxi] Diclofenac, IM (potential for scarring): Tarloff D, Lamacraft G, Joubert G. The prevalence of skin scars in patients previously given intramuscular diclofenac injections attending the Pain Clinic at Universitas Academic Hospital, Bloemfontein, South Africa. S Afr Med J. 2017 Jan 30;107(2):101-105. https://www.ncbi.nlm.nih.gov/pubmed/28220730

[xxii] Ward prescriptions for postoperative analgesia according to anticipated pain severity: The South African Society of Anaesthesiologists. South African Acute Pain Guidelines. SAJAA 2009;15(6):1-120. http://www.sasaweb.com/content/images/SASA_Pain_Guidelines.pdf
[xxiii] Patient controlled analgesia: Hudcova J, McNicol E, Quah C, Lau J, Carr DB. Patient controlled opioid analgesia versus conventional opioid analgesia for postoperative pain. Cochrane Database Syst Rev. 2006 Oct 18;(4):CD003348. Review. Update in: Cochrane Database Syst Rev. 2015;6:CD003348.. http://www.ncbi.nlm.nih.gov/pubmed/17054167
[xxiv] Diclofenac, IM (potential for scarring): Tarloff D, Lamacraft G, Joubert G. The prevalence of skin scars in patients previously given intramuscular diclofenac injections attending the Pain Clinic at Universitas Academic Hospital, Bloemfontein, South Africa. S Afr Med J. 2017 Jan 30;107(2):101-105. https://www.ncbi.nlm.nih.gov/pubmed/28220730
[xxv] Ringer Lactate, IV: National Department of Health: Affordable Medicines, EDP-Adult Hospital level. Medicine Review: Ringer Lactate for resuscitation in adults, updated review, August 2019. http://www.health.gov.za/
Ringer Lactate, IV: Antequera Martin AM, Barea Mendoza JA, Muriel A, Saez I, Chico-Fernandez M, Estrada-Lorenzo JM, et al. Buffered solutions versus 0.9% saline for resuscitation in critically ill adults and children. Cochrane Database Syst Rev. 2019 Jul 19;7:CD012247. https://www.ncbi.nlm.nih.gov/pubmed/31334842
Ringer Lactate, IV: Liu C, Lu G, Wang D, Lei Y, Mao Z, Hu P, Hu J, Liu R, Han D, Zhou F. Balanced crystalloids versus normal saline for fluid resuscitation in critically ill patients: A systematic review and meta-analysis with trial sequential analysis. Am J Emerg Med. 2019 Mar 1. pii: S0735-6757(19)30149-4. https://www.ncbi.nlm.nih.gov/pubmed/3085204
Ringer Lactate, IV: Brown RM, Wang L, Coston TD, Krishnan NI, Casey JD, Wanderer JP, et al. Balanced Crystalloids Versus Saline in Sepsis: A Secondary Analysis of the SMART Trial. Am J Respir Crit Care Med. 2019 Aug 27. doi: 10.1164/rccm.201903-0557OC. [Epub ahead of print]
Ringer Lactate, IV: Rochwerg B, Alhazzani W, Sindi A, Heels-Ansdell D, Thabane L, Fox-Robichaud A, et al. Fluid resuscitation in sepsis: A systematic review and network meta-analysis. Ann Intern Med. 2014;161(5):347–55. https://www.ncbi.nlm.nih.gov/pubmed/250474
[xxvi] Dantrolene, IV: Kolb ME, Horne ML, Martz R. Dantrolene in human malignant hyperthermia. Anesthesiology. 1982 Apr;56(4):254-62. https://www.ncbi.nlm.nih.gov/pubmed/7039419
Dantrolene, IV: Flewellen EH, Nelson TE, Jones WP, Arens JF, Wagner DL. Dantrolene dose response in awake man: implications for management of malignant hyperthermia. Anesthesiology. 1983 Oct;59(4):275-80. https://www.ncbi.nlm.nih.gov/pubmed/6614536
Dantrolene, IV: Larach MG, Brandom BW, Allen GC, Gronert GA, Lehman EB. Cardiac arrests and deaths associated with malignant hyperthermia in north america from 1987 to 2006: a report from the north American malignant hyperthermia registry of the malignant hyperthermia association of the United States. Anesthesiology. 2008 Apr;108(4):603-11. https://www.ncbi.nlm.nih.gov/pubmed/18362591
Dantrolene, IV: Chapin et al. Medscape: Malignant Hyperthermia Treatment & Management, 28 November 2018. [Internet][Accessed 2 December 2019] https://emedicine.medscape.com/article/2231150-treatment#d11
Dantrolene, IV: South African Medicines Formulary. 12th Edition. Division of Clinical Pharmacology. University of Cape Town, 2016.
[xxvii] Oxygen: Neal JM, Mulroy MF, Weinberg GL; American Society of Regional Anesthesia and Pain Medicine. American Society of Regional Anesthesia and Pain Medicine checklist for managing local anesthetic systemic toxicity: 2012 version. Reg Anesth Pain Med. 2012 Jan-Feb;37(1):16-8. http://www.ncbi.nlm.nih.gov/pubmed/22189574
Diazepam, IV: Neal JM, Mulroy MF, Weinberg GL; American Society of Regional Anesthesia and Pain Medicine. American Society of Regional Anesthesia and Pain Medicine checklist for managing local anesthetic systemic toxicity: 2012 version. Reg Anesth Pain Med. 2012 Jan-Feb;37(1):16-8. http://www.ncbi.nlm.nih.gov/pubmed/22189574
Adrenaline (epinephrine): Neal JM, Mulroy MF, Weinberg GL; American Society of Regional Anesthesia and Pain Medicine. American Society of Regional Anesthesia and Pain Medicine checklist for managing local anesthetic systemic toxicity: 2012 version. Reg Anesth Pain Med. 2012 Jan-Feb;37(1):16-8. http://www.ncbi.nlm.nih.gov/pubmed/22189574
[xxviii] Lipid emulsion (20%), IV: Jamaty C, Bailey B, Larocque A, Notebaert E, Sanogo K, Chauny JM. Lipid emulsions in the treatment of acute poisoning: a systematic review of human and animal studies. Clin Toxicol (Phila). 2010 Jan;48(1):1-27. http://www.ncbi.nlm.nih.gov/pubmed/20095812
Lipid emulsion (20%), IV: Neal JM, Mulroy MF, Weinberg GL; American Society of Regional Anesthesia and Pain Medicine. American Society of Regional Anesthesia and Pain Medicine checklist for managing local anesthetic systemic toxicity: 2012 version. Reg Anesth Pain Med. 2012 Jan-Feb;37(1):16-8. http://www.ncbi.nlm.nih.gov/pubmed/22189574
Lipid emulsion (20%), IV: National Department of Health, Essential Drugs Programme. Cost analysis report for intralipid 20% emulsion for local anesthetic systemic toxicity, 8 October 2015. http://health.gov.za/
[xxix] Ephedrine, IV: South African Medicines Formulary. 12th Edition. Division of Clinical Pharmacology. University of Cape Town, 2016.
[xxx] Phenylephrine, IV: South African Medicines Formulary. 12th Edition. Division of Clinical Pharmacology. University of Cape Town, 2016.
[xxxi] Labetalol, Scott DB. The use of labetalol in anaesthesia. Br J Clin Pharmacol. 1982 Jun;13(1 Suppl):133S-135S. http://www.ncbi.nlm.nih.gov/pubmed/7093097
Labetalol, IV: Varon J, Marik PE. Perioperative hypertension management. Vascular Health and Risk Management. 2008;4(3):615-627. http://www.ncbi.nlm.nih.gov/pubmed/18827911

[xxxii] Dexamethasone, IV: Carlisle JB, Stevenson CA. Drugs for preventing postoperative nausea and vomiting. Cochrane Database Syst Rev. 2006 Jul 19;(3):CD004125. http://www.ncbi.nlm.nih.gov/pubmed/16856030
Ondansetron, IV: Carlisle JB, Stevenson CA. Drugs for preventing postoperative nausea and vomiting. Cochrane Database Syst Rev. 2006 Jul 19;(3):CD004125. http://www.ncbi.nlm.nih.gov/pubmed/16856030
Promethazine, IV: Carlisle JB, Stevenson CA. Drugs for preventing postoperative nausea and vomiting. Cochrane Database Syst Rev. 2006 Jul 19;(3):CD004125. http://www.ncbi.nlm.nih.gov/pubmed/16856030
[xxxiii] Ondansetron, IV/IM (PONV): Zhang D, Shen Z, You J, Zhu X, Tang QF. Effect of ondansetron in preventing postoperative nausea and vomiting under different conditions of general anesthesia: a preliminary, randomized, controlled study. Ups J Med Sci. 2013 May;118(2):87-90. https://www.ncbi.nlm.nih.gov/pubmed/23441598
Ondansetron, IV/IM (PONV): South African Medicines Formulary. 12th Edition. Division of Clinical Pharmacology. University of Cape Town, 2016.
[xxxiv] Sodium citrate, solution: Paranjothy S, Griffiths JD, Broughton HK, Gyte GM, Brown HC, Thomas J. Interventions at caesarean section for reducing the risk of aspiration pneumonitis. Cochrane Database Syst Rev. 2014 Feb 5;2:CD004943. http://www.ncbi.nlm.nih.gov/pubmed/24497372
Sodium citrate solution: National Department of Health, Essential Drugs Programme. Medicine review: Sodium citrate solution to reduce the risk of aspiration pneumonitis in patients undergoing Caeserean section. September 2015. http://health.gov.za/
[xxxv] Timing of anticoagulants: The BRIDGE Study Investigators .Bridging Anticoagulation: Is it Needed When Warfarin Is Interrupted Around the Time of Surgery or a Procedure? Circulation 2012;125:e496-e498. http://www.ncbi.nlm.nih.gov/pubmed/22451610
Timing of anticoagulants: Horlocker TT, Vandermeuelen E, Kopp SL, Gogarten W, Leffert LR, Benzon HT. Regional Anesthesia in the Patient Receiving Antithrombotic or Thrombolytic Therapy: American Society of Regional Anesthesia and Pain Medicine Evidence-Based Guidelines (Fourth Edition). Reg Anesth Pain Med. 2018 Apr;43(3):263-309. https://www.ncbi.nlm.nih.gov/pubmed/29561531
[xxxvi] Bupivicaine, 0.5%: South African Medicines Formulary. 12th Edition. Division of Clinical Pharmacology. University of Cape Town, 2016.
[xxxvii]Lidocaine 1% or 2%: South African Medicines Formulary. 12th Edition. Division of Clinical Pharmacology. University of Cape Town, 2016.
Lidocaine 2% plus adrenaline: South African Medicines Formulary. 12th Edition. Division of Clinical Pharmacology. University of Cape Town, 2016.
Bupivicaine 0.5%: South African Medicines Formulary. 12th Edition. Division of Clinical Pharmacology. University of Cape Town, 2016.
[xxxviii] Lidocaine topical jelly: South African Medicines Formulary. 12th Edition. Division of Clinical Pharmacology. University of Cape Town, 2016.
[xxxix] Lidocaine topical spray: South African Medicines Formulary. 12th Edition. Division of Clinical Pharmacology. University of Cape Town, 2016.
[xl] Lidocaine/prilocaine, topical cream, 2.5/2.5%.: Sharma SK, Gajraj NM, Sidawi JE, Lowe K. EMLA cream effectively reduces the pain of spinal needle insertion. Regional anesthesia. 1996 Nov-Dec;21(6):561-4. http://www.ncbi.nlm.nih.gov/pubmed/8956393

CHAPTER 13

MUSCULOSKELETAL CONDITIONS

13.1 ARTHRITIS, RHEUMATOID (RA)

M05.80-89/M05.90-99/M06.00-09/M06.80-09/M06.90-99/M08.30-39/M08.40-49/ M08.80-89/M08.90-99

DESCRIPTION

A chronic, inflammatory, systemic condition with a fluctuating course. It may affect many organs, but the joints are predominantly affected. Characteristic joint manifestations are:

» Swelling or fluid, affecting at least three joint areas simultaneously.
» Pain.
» Limited movement with morning stiffness >1 hour, which improves with activity. This helps distinguish osteoarthritis from rheumatoid arthritis.
» Destruction and deformity of affected joints.
» The small joints of the fingers and hands, with the exception of the distal interphalangeal joints, are usually involved, although any joint can be involved.
» Arthritis is typically symmetrical.

GENERAL MEASURES

Manage by co-ordinated multidisciplinary care.
The primary objective is to improve and maintain functional status.
Early use of non-drug measures, especially nursing, physiotherapy and occupational therapy, is essential.
Acute flare-ups: rest affected joints and consider the use of day and/or night splints.
Obtain a baseline complete blood count, serum creatinine, alanine aminotransferase (ALT), and erythrocyte sedimentation rate (ESR) or C-reactive protein (CRP) in all patients.
Obtain X-rays of the hands and wrists, as well as both forefeet to include the metatarsophalangeal joints as a baseline for evaluating change in the joints during treatment.

MEDICINE TREATMENT

All patients with suspected RA should be seen by a specialist. Evaluate all patients with suspected RA for disease-modifying anti-rheumatic drug (DMARD):

- Methotrexate (preferred initial therapy)
- Chloroquine sulphate
- Sulfasalazine

Monitoring response to DMARDs:

» Assess response to DMARD therapy by monitoring the number of swollen and tender joints, restricted to 28 joints (shoulders, elbows, wrists, 5 metacarpophalangeal joints, 5 proximal interphalangeal joints and knees bilaterally) together with ESR or CRP.

» If there is poor response to one DMARD, after 3 months, add another DMARD. *LoE:II*[i]

» Patients on DMARDs must be monitored regularly for toxicity, as outlined below:

- Methotrexate, oral, 7.5 mg once per week. Specialist consultation.
  - Increase dose gradually to a maximum of 25 mg per week.
  - Monitor: ALT and FBC before and 12 weekly during treatment.

AND

- Folic acid, oral, 5 mg per week at least 24 hours after the methotrexate dose.

LoE:II[ii]

AND/OR

- Chloroquine sulphate, oral, 150 mg (as base) daily for 5 days of each week.
  - Do ophthalmic examination at baseline within the first year of treatment and annually thereafter, to monitor for ocular damage.

AND/OR

- Sulfasalazine, oral, 500 mg 12 hourly with meals.
  - Gradually increase over one month from 500 mg to 1 g 12 hourly.
  - FBC and ALT monthly for first 3 months then every 3–6 months.

LoE:III[iii]

Oral corticosteroids

Systemic corticosteroids are effective at relieving symptoms in RA and have been shown to modify the course of the disease, but long-term use is discouraged because this is associated with considerable toxicity, notably osteoporosis, which is very common in patients with RA.

Indications:

» As bridging therapy while waiting for DMARDs to take effect.

» Acute disease flares.

» Severe extra-articular manifestations, e.g. scleritis.

- Corticosteroids (intermediate-acting) e.g.:
- Prednisone, oral, 40 mg daily for 2 weeks.
  - Thereafter gradually reduce the dose to ≤7.5 mg daily. (Refer to Appendix II for an example of a dose reduction regimen).
  - Discontinue at 3–6 months.
  - If disease flares after stopping corticosteroids DMARD therapy should be optimised. *LoE:II*[iv]

Patients requiring corticosteroids for longer than 3 months should be educated to take in enough calcium in their diet.

For pain:

- Paracetamol, oral, 500 mg to 1 g, 4 to 6 hourly as required (to a maximum of 4 g in 24 hours).
  - Maximum dose: 15 mg/kg/dose.

NSAIDs

NSAIDs are used for symptomatic relief in patients with active inflammation and pain. They have no long-term disease modifying effects.
NSAID dose should be reduced and then stopped once the DMARDs have taken effect.
Reduce NSAID doses in the elderly.
NSAIDs are relatively contra-indicated in patients with significantly impaired renal function, i.e. eGFR <60 mL/minute.

CAUTION
Concomitant use of more than one oral NSAID has no additional clinical benefit and only increases toxicity.
Use of all NSAIDs is associated with increased risks of gastrointestinal bleeding, renal dysfunction, and cardiovascular events (stroke and myocardial infarction).
NSAIDs should be used judiciously at the lowest effective dose for the shortest duration. Explore and manage exacerbating factors for pain. See Section 26.1: Chronic pain.
Do not use NSAID in pregnancy or while breastfeeding.

- NSAID, e.g.:
- Ibuprofen, oral, 400 mg 8 hourly with meals. *LoE:I[v]*

An extra **night-time** dose of an NSAID may be added in some patients with severe nocturnal pain/morning stiffness.

Note: When an additional night-time dose is added to the patient's regimen, the risk of NSAID toxicity increases. A reduction in the daytime dose of NSAIDs is recommended as the night-time dose will often exceed the recommended total daily NSAID dose.
If a reduction in daytime dose causes increased pain, then the use of the night-time dose must be for the shortest period possible.

In high-risk patients: >65 years of age; history of peptic ulcer disease; on concomitant warfarin, aspirin, or corticosteroids:

ADD *LoE:II[vi]*

- PPI, e.g.:
- Lansoprazole, oral, 30 mg daily while on an NSAID.

Adjunct for pain control:

- Amitriptyline, oral, 10–25 mg at night.

- Titrate dose according to response.
- Initial dose in the elderly: 10 mg at night.
- Maximum dose: 75 mg at night.
- Use with caution in patients with angle closure glaucoma, prostatic hypertrophy and the elderly.

Intra-articular corticosteroids
Consider only in cases where a few joints are very actively inflamed.
To be prescribed by a specialist.
Not more than 2–3 injections per year per joint are recommended.
- Intra-articular corticosteroid, e.g.:
- Methylprednisolone acetate, 20–80 mg depending on joint size.

LoE:III[vii]

REFERRAL
» At initial diagnosis.
» Disease activity cannot be controlled with the measures as mentioned.
» Compression neuropathy.
» For joint replacement.

Urgent
» Rupture of tendons.
» Scleritis.
» Unstable upper cervical spine.
» Vasculitis.
» Cricoarytenoid joint involvement with hoarseness and inspiratory stridor.

13.2 ARTHRITIS, SEPTIC AND OSTEOMYELITIS, ACUTE
M00.90-99/M86.10-19

DESCRIPTION
Septic arthritis is typically an acute infective condition involving one or more joints. The joint is hot, swollen, very painful on movement, and with restricted movements.
Acute osteomyelitis typically involves the long bones or the vertebrae.
Signs of systemic infection are usually present. The infection is usually bloodborne, but may follow trauma. The course may be acute or protracted. The commonest causative organism is *Staphylococcus aureus*. *N. gonorrhoeae* is an important cause of septic arthritis.
Note: Acute gout and haemophiliacs with bleeding into joints may mimic septic arthritis.

GENERAL MEASURES
Baseline X-ray.
Rest and immobilisation.

Septic arthritis: Drainage is important. Discuss with a specialist.

MEDICINE TREATMENT

Empiric antibiotic therapy

Therapy is directed against *S. aureus* unless there is evidence of urethritis or PID, in which case gonococcal infection should be covered.

It is crucial to obtain cultures of blood, joint or aspirate of osteomyelitis focus before administering antibiotics.

- Cefazolin, IV, 2 g 8 hourly for 4 weeks. *LoE:II*[viii]

After 2 weeks of IV therapy, a change to oral therapy may be considered in patients with a good clinical response:

- Flucloxacillin, oral, 1 g 6 hourly to complete the 4 weeks' treatment.

Severe penicillin allergy: (Z88.0)

- Clindamycin, IV, 600 mg 8 hourly.

After 2 weeks of IV therapy, a change to oral therapy may be considered in patients with a good clinical response:

- Clindamycin, oral, 450mg 8 hourly to complete the 4 weeks' treatment.

LoE:III[ix]

For gonococcal arthritis A54.4+ + (M01.30-39*)

- Ceftriaxone, IV, 1 g daily for 1 week.

AND

- Azithromycin, oral, 1 g, as a single dose. *LoE:III*[x]

Severe penicillin allergy: (Z88.0)

Refer.

Analgesia

- NSAID, e.g.:
- Ibuprofen, oral, 400 mg 8 hourly with meals. *LoE:I*[xi]

AND/OR

- Paracetamol, oral, 500 mg to 1 g, 4 to 6 hourly as required (to a maximum of 4 g in 24 hours).
  - Maximum dose: 15 mg/kg/dose.

REFERRAL

» Acute osteomyelitis/ septic arthritis for early drainage by specialist surgeon.
» If pyrexia persists despite adequate antibiotic therapy, a sub-periosteal abscess must be sought and drained by a specialist surgeon.
» Chronic osteomyelitis.
» Pathological fractures.

13.3 OSTEOARTHRITIS

M13.00-19/M16.0-9/M17.0-9/M18.0-9/M19.00-09/M19.80-99

DESCRIPTION

A disorder typically affecting weight-bearing joints and the hand (distal and

proximal interphalangeals, and first metacarpophalangeal joints).
Signs and symptoms include:
» Pain on effort, relieved by rest.
» Morning stiffness, lasting < 30 minutes.
» Limited movement.
» Joint swelling (effusions and/or osteophytes).

GENERAL MEASURES

Weight reduction.
Exercise: postural and non-weight bearing. Quadriceps strengthening for knee involvement.
Support and alleviate weight bearing of affected joints, i.e. walking stick.
Physiotherapy and/or occupational therapy.

MEDICINE TREATMENT

When only pain relief is required:

- Paracetamol, oral, 500 mg to 1 g, 4 to 6 hourly as required (to a maximum of 4 g in 24 hours).
  - Maximum dose: 15 mg/kg/dose.

If ineffective:

ADD

- NSAID, e.g.:
- Ibuprofen, oral, 400 mg 8 hourly with meals. *LoE:I*[xii]

As many of these patients, particularly the elderly, have concomitant medical conditions such as cardiovascular, gastrointestinal disease or renal function impairment, NSAIDs must be used with caution.

Patients on aspirin for cardiovascular risk reduction should take this agent 30 minutes before the 1st dose of NSAID in the morning, as taking aspirin and NSAID at the same time may reduce aspirin's efficacy. *LoE:III*[xiii]

In high-risk patients: >65 years of age; history of peptic ulcer disease; or on concomitant warfarin, aspirin or corticosteroids:

ADD *LoE:II*[xiv]

- PPI, e.g.:
- Lansoprazole, oral, 30 mg daily.

CAUTION

Use of all NSAIDs is associated with increased risks of gastrointestinal bleeding, renal dysfunction, and cardiovascular events (stroke and myocardial infarction).
NSAIDs should be used judiciously at the lowest effective dose for the shortest duration. Explore and manage exacerbating factors for pain. See Section 26.1: Chronic pain.
Do not use NSAID in pregnancy or while breastfeeding.

If ineffective:
Adjunct for pain control:
- Amitriptyline, oral, 10–25 mg at night.
  - Titrate dose according to response.
  - Initial dose in the elderly: 10 mg at night.
  - Maximum dose: 75 mg at night.

Intra-articular corticosteroids
Consider in cases where a joint is actively inflamed.
To be prescribed and administered by a specialist only.
Not more than 2–3 injections per year per joint are recommended.
- Intra-articular corticosteroid, e.g.:
- Methylprednisolone acetate, 20–80 mg depending on joint size.

LoE:III[xv]

REFERRAL
» For consideration for joint replacement.
» Intractable pain.
» Neurogenic compression.

13.4 GOUT
M10.90-99

DESCRIPTION
A metabolic disease in which uric acid crystal deposition occurs in joints and other tissues.
Gout is managed in the following three stages:
i) Treating the acute attacks;
ii) Prevention of acute flares;
iii) Lowering excessive uric acid to prevent flares and tissue deposition of urate crystals.

LoE:III[xvi]

Acute gout:
Joint involvement is characterised by recurrent attacks of acute arthritis, which usually affects one joint, and is accompanied by extreme pain and tenderness, swelling, redness, and local heat.
» The inflammation may extend beyond the joint.
» In many patients the first metatarsophalangeal joint is initially involved.
» The instep, ankle, heel, and knee are also commonly involved.
» Bursae (such as the olecranon) may be involved.

Chronic gout:
Gout with one or more of the following:
» uric acid deposits in and around joints, bursae and cartilages of the extremities (tophi)
» initial involvement of the first metatarsophalangeal joint in most patients
» involvement of the instep, ankle, heel and knee

» involvement of bursae (such as the olecranon)
» significant periarticular inflammation
» bone destruction
» prolongation of attacks, often with reduction in pain severity
» incomplete resolution between attacks

GENERAL MEASURES

Acute gout:
Rest and immobilisation.

Chronic gout:
Lifestyle modification, including high fluid intake.
Avoid alcohol intake.
If possible, avoid diuretics, or use the lowest dose possible.

MEDICINE TREATMENT

ACUTE GOUT:

Initiate treatment as early as possible in an acute attack:

- NSAID, e.g.:
- Ibuprofen, oral, 400 mg 8 hourly with meals. *LoE:I*[xvii]

In high-risk patients: > 65 years of age; history of peptic ulcer disease; on concomitant warfarin, aspirin, or corticosteroids:

ADD *LoE:II*[xviii]

- PPI, e.g.:
- Lansoprazole, oral, 30 mg daily while on an NSAID.

If NSAIDS are contraindicated, e.g. warfarin therapy and renal dysfunction:

- Corticosteroids (intermediate-acting) e.g.:
- Prednisone, oral, 40 mg daily for 5 days.

CHRONIC GOUT:

If possible, avoid known precipitants and medicines that increase uric acid, including:
» low dose aspirin,
» ethambutol,
» pyrazinamide, and
» thiazide and loop diuretics.

If diagnosis uncertain, joint aspiration with microscopy for crystal analysis is recommended.
Investigate for and treat secondary causes (e.g. haematological malignancies) where clinically indicated.
Measure serum creatinine and urate.
Serum urate may be normal during acute attacks.

Urate lowering therapy
Urate lowering therapy is recommended in the following circumstances:

» >2 acute attacks per year
» chronic tophaceous gout
» urate renal stones
» urate nephropathy

When the acute attack has settled, i.e. usually after 2 weeks:

- Allopurinol, oral, 100 mg daily.
  - Increase monthly by 100 mg according to serum urate levels.
  - Titrate dose to reduce serum urate to <0.35 mmol/L.
  - Allopurinol dosage is dependent on severity of disease and serum urate concentration. Doses in excess of 300 mg should be administered in divided doses. *LoE:III*[xix]
  - Maximum dose: 900 mg per day.
  - Elderly: start with 50 mg daily.
  - Renal impairment: Adjust dose according to renal function.
    - eGFR 30–60 mL/minute: start with 50 mg daily.
    - eGFR <10 mL/minute: consult a specialist. *LoE:III*[xx]

Caution in prescribing allopurinol to patients with renal impairment as they have an increased risk of a hypersensitivity reaction. Immediate cessation of allopurinol if rash or fever occurs.

LoE:III[xxi]

Prophylaxis to prevent breakthrough gout attacks:

An increase incidence of gout flares is associated with initiation of urate lowering therapy. Thus, colchicine or NSAIDs is recommended as anti-inflammatory prophylaxis when initiating allopurinol.

Anti-inflammatory prophylaxis should be discontinued at **6 months** provided gout symptoms have resolved**.**

- NSAID, e.g.: *LoE:I*[xxii]
- Ibuprofen, oral, 400 mg 8 hourly with meals.
  - Monitor renal function, as clinically indicated.

OR

Colchicine, oral, 0.5 mg 12 hourly for 6 months. *LoE:III*[xxiii]

- eGFR < 50 mL/minute: consult a specialist

CAUTION

Concomitant use of more than one oral NSAID has no additional clinical benefit and only increases toxicity.

Use of all NSAIDs is associated with increased risks of gastrointestinal bleeding, renal dysfunction, and cardiovascular events (stroke and myocardial infarction).

NSAIDs should be used judiciously at the lowest effective dose for the shortest duration. Explore and manage exacerbating factors for pain. See Section 26.1: Chronic pain.

Do not use NSAID in pregnancy or while breastfeeding.

In high-risk patients: i.e. patients > 65 years of age, or with a history of peptic ulcer disease, or on concomitant warfarin, aspirin or corticosteroids:

ADD *LoE:II*[xxiv]

- PPI, e.g.:
- Lansoprazole, oral, 30 mg daily.

Do not stop urate lowering drugs during an acute attack.

REFERRAL

» No response to treatment despite adequate adherence.
» Suspected secondary gout.
» Non-resolving tophaceous gout.

13.5 SERONEGATIVE SPONDYLARTHRITIS

M45.X0-X9/M47.9099

DESCRIPTION

A group of diseases in which the rheumatoid factor is usually negative and the spine is often involved. These disorders have certain similar clinical features and occur predominantly in individuals with HLA-B27 antigen. The rheumatological manifestations in these disorders are variable, typically including asymmetrical lower-limb arthritis, sacro-iliitis, spinal inflammation (spondylitis), and enthesitis (e.g., Achilles tendonitis). The spondyloarthritides include ankylosing spondylitis, reactive arthritis, psoriatic arthropathy, and arthritis associated with inflammatory bowel disease. Extra-articular manifestations occur, especially uveitis, in about one third of patients.

GENERAL MEASURES

Physiotherapy to prevent spine deformity.

MEDICINE TREATMENT

Initiate treatment with NSAIDs.

- NSAID, e.g.:
- Ibuprofen, oral, 400 mg 8 hourly with meals. *LoE:I*[xxv]

In high-risk patients: i.e. patients > 65 years of age, or with a history of peptic ulcer disease, or on concomitant warfarin, aspirin or corticosteroids:

ADD *LoE:II*[xxvi]

- PPI, e.g.:
- Lansoprazole, oral, 30 mg daily.

REFERRAL

» Uveitis, to an ophthalmologist.
» Psoriasis, to dermatologist and rheumatologist

» Arthritis refractory to NSAIDs, to a rheumatologist.
» Deformity at diagnosis, to a rheumatologist.

13.5.1 ARTHRITIS, REACTIVE

M02.30-39

DESCRIPTION

A spondylarthritis often preceded by enteric or urogenital infections 1–4 weeks before the arthritis and occurring predominantly in individuals with HLA-B27 antigen.
It is a clinical diagnosis with no laboratory test or radiographic findings.
It occurs more commonly in HIV infection.
It is usually self-limiting.

MEDICINE TREATMENT

- NSAID, e.g.:
- Ibuprofen, oral, 400 mg 8 hourly with meals. *LoE:I*[xxvii]

In high-risk patients: i.e. patients > 65 years of age, or with a history of peptic ulcer disease, or on concomitant warfarin, aspirin or corticosteroids:

ADD *LoE:II*[xxviii]

- PPI, e.g.:
- Lansoprazole, oral, 30 mg daily.

If urethritis is present, treatment may prevent further episodes of arthritis:

- Ceftriaxone, IM, 250 mg as a single dose.
  - For ceftriaxone IM injection: Dissolve ceftriaxone 250 mg in 0.9 mL lidocaine 1% without epinephrine (adrenaline).

AND

- Azithromycin, oral, 1 g, as a single dose.

LoE:II[xxix]

13.6 SYSTEMIC LUPUS ERYTHEMATOSUS (SLE)

M32.9

These patients need to be managed by a specialist.

GENERAL MEASURES

Education regarding the disease and complications.
Avoid cigarette smoking as it is a trigger for lupus.
Sun protective barrier creams are often indicated.
Regularly monitor urine for blood and protein.
Provide advice regarding family planning as pregnancy may cause a lupus flare.

MEDICINE TREATMENT

MILD DISEASE

For pain:

- Paracetamol, oral, 500 mg to 1 g, 4 to 6 hourly as required (to a maximum of 4 g in 24 hours).
  - Maximum dose: 15 mg/kg/dose.

AND/OR

- NSAID, e.g.:
- Ibuprofen, oral, 400 mg 8 hourly with meals. *LoE:I*[xxx]

In high-risk patients: i.e. patients > 65 years of age, or with a history of peptic ulcer disease, or on concomitant warfarin, aspirin or corticosteroids:

ADD *LoE:II*[xxi]

- PPI, e.g.:
- Lansoprazole, oral, 30 mg daily.

To suppress disease activity

- Chloroquine sulphate, oral, 150 mg (as base) daily for 5 days of each week.
  - Do ophthalmic examination at baseline within the first year of treatment and annually, to monitor for ocular damage.

LoE:I[xxii]

Corticosteroids

Initiate therapy in patients with life threatening manifestations and organ involvement.

- Corticosteroids (intermediate-acting) e.g.:
- Prednisone, oral, 2 mg/kg daily, initial dose.
  - Taper to the lowest maintenance dose after a response has been obtained. Refer to Appendix II for an example of a dose reduction regimen.
  - Usual maintenance dose: 10 mg daily.

Patients requiring corticosteroids for >3 months (long-term) should be managed for secondary prevention of osteoporotic fractures. See Section 8.12: Osteoporosis.

Additional immunosuppressive therapy

Is often required for life-threatening disease, particularly kidney and CNS involvement. These medicines should be initiated by a specialist and regular FBC monitoring should be done.

- Azathioprine, oral, 1 mg/kg daily, titrated to a maximum of 3 mg/kg daily.

OR *LoE:III*

Cyclophosphamide, oral, 100 mg daily, titrated to a maximum of 200 mg daily (or 1–3 mg/kg daily).

LoE:III

RAYNAUD'S PHENOMENON I73.0

- Amlodipine, oral, 5 mg daily.

LoE:II[xxxiii]

ANTIPHOSPHOLIPID ANTIBODY SYNDROME

- Aspirin, oral, 150 mg daily.

Patients with previous thrombo-embolic episodes should receive lifelong warfarin (target INR 3 to 4).

LoE:III

Hormonal therapy in women

The use of oral contraceptives is controversial.
Until there is clarity it is advisable to use either progesterone-only, or low dose oestrogens, or non-hormonal methods.

REFERRAL

» All patients to a specialist for initial assessment.
» Lupus flare.
» Nephritis for renal biopsy.
» Persistent haematological derangements i.e. thrombocytopaenia.
» Neurological manifestations of lupus.

References:

[i] DMARDs - 3 month time point: Aletaha D, Alasti F, Smolen JS. Optimisation of a treat-to-target approach in rheumatoid arthritis: strategies for the 3-month time point. Ann Rheum Dis. 2016 Aug;75(8):1479-85. https://www.ncbi.nlm.nih.gov/pubmed/26420577

DMARDs - 3 month time point: Smolen JS, Landewé R, Bijlsma J, Burmester G, Chatzidionysiou K, Dougados M, et al. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2016 update. Ann Rheum Dis. 2017 Jun;76(6):960-977. https://www.ncbi.nlm.nih.gov/pubmed/28264816

DMARDs - 3 month time point: Singh JA, Saag KG, Bridges SL Jr, Akl EA, Bannuru RR, Sullivan MC, et al. 2015 American College of Rheumatology Guideline for the Treatment of Rheumatoid Arthritis. Arthritis Rheumatol. 2016 Jan;68(1):1-26. https://www.ncbi.nlm.nih.gov/pubmed/26545940

[ii] Folic acid: Shea B, Swinden MV, TanjongGhogomu E, Ortiz Z, Katchamart W, Rader T, Bombardier C, Wells GA, Tugwell P. Folic acid and folinic acid for reducing side effects in patients receiving methotrexate for rheumatoid arthritis. Cochrane Database Syst Rev. 2013 May 31;5:CD000951. http://www.ncbi.nlm.nih.gov/pubmed/24737913

[iii] Sulfasalazine, oral: South African Medicines Formulary. 12th Edition. Division of Clinical Pharmacology. University of Cape Town, 2016.

[iv] Corticosteroids, oral (3-6 months): Boers M, Verhoeven AC, Markusse HM, van de Laar MA, Westhovens R, van DenderenJC, van Zeben D, Dijkmans BA, Peeters AJ, Jacobs P, van den Brink HR, Schouten HJ, van der Heijde DM, Boonen A, van der Linden S. Randomised comparison of combined step-down prednisolone, methotrexate and sulphasalazine with sulphasalazine alone in early rheumatoid arthritis. Lancet. 1997 Aug 2;350(9074):309-18. Erratum in: Lancet 1998 Jan 17;351(9097):220. http://www.ncbi.nlm.nih.gov/pubmed/9251634

Corticosteroids, oral (3-6 months):Goekoop-Ruiterman YP, de Vries-Bouwstra JK, Allaart CF, van Zeben D, KerstensPJ, Hazes JM, Zwinderman AH, Ronday HK, Han KH, Westedt ML, Gerards AH, van Groenendael JH, Lems WF, van KrugtenMV, Breedveld FC, Dijkmans BA. Clinical and radiographic outcomes of four different treatment strategies in patients with early rheumatoid arthritis (the BeSt study): a randomized, controlled trial. Arthritis Rheum. 2005 Nov;52(11):3381-90.http://www.ncbi.nlm.nih.gov/pubmed/16258899

Corticosteroids, oral (3-6 months): Singh JA, Saag KG, Bridges SL Jr, Akl EA, Bannuru RR, Sullivan MC, Vaysbrot E, McNaughton C, Osani M, Shmerling RH, Curtis JR, Furst DE, Parks D, Kavanaugh A, O'Dell J, King C, Leong A, Matteson EL, Schousboe JT, Drevlow B, Ginsberg S, Grober J, St Clair EW, Tindall E, Miller AS, McAlindon T. 2015 American College of Rheumatology Guideline for the Treatment of Rheumatoid Arthritis. Arthritis Rheumatol. 2016 Jan;68(1):1-26.http://www.ncbi.nlm.nih.gov/pubmed/26545940

Corticosteroids, oral: South African Medicines Formulary. 12th Edition. Division of Clinical Pharmacology. University of Cape Town, 2016.

[v] NSAIDs as a therapeutic class (diclofenac, naproxen, ibuprofen): Affordable Medicines, EDP-Adult Hospital level. NSAIDs – comparative review of efficacy and safety, 15 January2018. http://www.health.gov.za

NSAIDs as a therapeutic class (diclofenac, naproxen, ibuprofen): Van Walsem A, Pandhi S, Nixon RM, Guyot P, Karabis A, Moore RA. Relative benefit-risk comparing diclofenac to other traditional non-steroidal anti-inflammatory drugs and cyclooxygenase-2 inhibitors in patients with osteoarthritis or rheumatoid arthritis: a network meta-analysis. Arthritis Research & Therapy 2015;17:66. https://www.ncbi.nlm.nih.gov/pubmed/25879879

NSAIDs as a therapeutic class (diclofenac, naproxen, ibuprofen): Nissen SE, Yeomans ND, Solomon DH, Lüscher TF, et al. Cardiovascular Safety of Celecoxib, Naproxen, or Ibuprofen for Arthritis. N Engl J Med 2016;375:2519-29. https://www.ncbi.nlm.nih.gov/pubmed/28379793

NSAIDs as a therapeutic class (diclofenac, naproxen, ibuprofen): Coxib and traditional NSAID Trialists' (CNT) Collaboration. Vascular and upper gastrointestinal effects of non-steroidal anti-inflammatory drugs: meta-analyses of individual participant data from randomised trials. Lancet 2013; 382: 769–79. https://www.ncbi.nlm.nih.gov/pubmed/23726390

NSAIDs as a therapeutic class (diclofenac, naproxen, ibuprofen): Trelle S, Reichenbach S, Wandel S, Hildebrand P, Tschannen B, et al. Cardiovascular safety of non-steroidal anti-inflammatory drugs: network meta-analysis. BMJ 2011;342:c7086. https://www.ncbi.nlm.nih.gov/pubmed/21224324

NSAIDs as a therapeutic class (diclofenac, naproxen, ibuprofen): Ong CKS, Lirk P, Tan Ch, Seymour RA. An evidence-based update on nonsteroidal anti-inflammatory drugs. Clinical Medicine and Research 2007; 5(1):19-34. https://www.ncbi.nlm.nih.gov/pubmed/17456832

NSAIDs as a therapeutic class (diclofenac, naproxen, ibuprofen): Stam WB, Jansen JP, Taylor SD. Efficacy of etoricoxib, lumiracoxib, non-selective NSAIDs, and acetaminophen in osteoarthritis: a mixed treatment comparison. The Open Rheumatology Journal 2012; 6:6-20. https://www.ncbi.nlm.nih.gov/pubmed/22582102

NSAIDs as a therapeutic class (diclofenac, naproxen, ibuprofen): Bello AE, Holt RJ. Cardiovascular risk with non-steroidal anti-inflammatory drugs: clinical implications. Drug Saf. 2014 Nov;37(11):897-902. https://www.ncbi.nlm.nih.gov/pubmed/25079141

NSAIDs as a therapeutic class (diclofenac, naproxen, ibuprofen): South African Medicines Formulary. 12th Edition. Division of Clinical Pharmacology. University of Cape Town, 2016.

[vi] PPI (high risk patients on chronic NSAID therapy): McQuaid KR ,Laine L . Systemic review and meta-analysis of adverse events of low-dose aspirin and clopidogrel in randomized controlled trials. Am J Med 2006;119:624–38. http://www.ncbi.nlm.nih.gov/pubmed/16887404

PPI (high risk patients on chronic NSAID therapy): Serrano P, Lanas A, Arroyo MT, Ferreira IJ. Risk of upper gastrointestinal bleeding in patients taking low-dose aspirin for the prevention of cardiovascular diseases. Aliment PharmacolTher. 2002 Nov;16(11):1945-53. http://www.ncbi.nlm.nih.gov/pubmed/12390104

PPI (high risk patients on chronic NSAID therapy): Lanza FL, Chan FK, Quigley EM; Practice Parameters Committee of the American College of Gastroenterology. Guidelines for prevention of NSAID-related ulcer complications. Am J Gastroenterol. 2009 Mar;104(3):728-38. http://www.ncbi.nlm.nih.gov/pubmed/19240698

PPI (high risk patients on chronic NSAID therapy): Narum S, Westergren T, Klemp M. Corticosteroids and risk of gastrointestinal bleeding: a systematic review and meta-analysis. BMJ Open. 2014 May15;4(5):e004587. https://www.ncbi.nlm.nih.gov/pubmed/24833682

PPI (high risk patients on chronic NSAID therapy): Scarpignato C, Gatta L, Zullo A, Blandizzi C; SIF-AIGO-FIMMG Group; Italian Society of Pharmacology, the Italian Association of Hospital Gastroenterologists, and the Italian Federation of General Practitioners. Effective and safe proton pump inhibitor therapy in acid-related diseases - A position paper addressing benefits and potential harms of acid suppression. BMC Med. 2016 Nov 9;14(1):179. https://www.ncbi.nlm.nih.gov/pubmed/27825371

[vii] Intra-articular corticosteroids: South African Medicines Formulary. 12th Edition. Division of Clinical Pharmacology. University of Cape Town, 2016.

[viii] Cefazolin, IV: Loubet P, Burdet C, Vindrios W, Grall N, Wolff M, Yazdanpanah Y, AndremontA, Duval X, Lescure FX. Cefazolin versus anti-staphylococcal penicillins for treatment of methicillin-susceptible Staphylococcus aureus bacteraemia: a narrative review. ClinMicrobiol Infect. 2017 Jul 8.pii: S1198-743X(17)30358-0.https://www.ncbi.nlm.nih.gov/pubmed/28698037

Cefazolin, IV: Bai AD, Showler A, Burry L, Steinberg M, Ricciuto DR, Fernandes T, Chiu A, Raybardhan S, Science M, Fernando E, Tomlinson G, Bell CM, Morris AM. Comparative effectiveness of cefazolin versus cloxacillin as definitive antibiotic therapy for MSSA bacteraemia: results from a large multicentre cohort study. J Antimicrob Chemother. 2015 May;70(5):1539-46. https://www.ncbi.nlm.nih.gov/pubmed/25614044

Cefazolin, IV: Perovic O, Singh-Moodley A, Govender NP, Kularatne R, Whitelaw A, Chibabhai V, Naicker P, Mbelle N, Lekalakala R, Quan V, Samuel C, Van Schalkwyk E; for GERMS-SA. A small proportion of community-associated methicillin-resistant Staphylococcus aureus bacteraemia, compared to healthcare-associated cases, in two South African provinces. Eur J Clin Microbiol Infect Dis. 2017 Dec;36(12):2519-2532. https://www.ncbi.nlm.nih.gov/pubmed/28849285

Cefazolin, IV: Stevens DL, Bisno AL, Chambers HF, Dellinger EP, Goldstein EJ, Gorbach SL, Hirschmann JV, Kaplan SL, Montoya JG, Wade JC; Infectious Diseases Society of America. Practice guidelines for the diagnosis and management of skin and soft tissue infections: 2014 update by the Infectious Diseases Society of America. Clin Infect Dis. 2014 Jul 15;59(2):e10-52. https://www.ncbi.nlm.nih.gov/pubmed/24973422

[ix] Clindamycin, oral dose: Bouazza N, Pestre V, Jullien V, Curis E, Urien S, Salmon D, Tréluyer JM. Population pharmacokinetics of clindamycin orally and intravenously administered in patients with osteomyelitis. Br J Clin Pharmacol. 2012 Dec;74(6):971-7.http://www.ncbi.nlm.nih.gov/pubmed/22486719

Clindamycin, oral dose: Wasserman et al. South African antibiotic stewardship programme (SAASP): A pocket guide to antibiotic prescribing for adults in South Africa, 2014.http://www.fidssa.co.za/images/SAASP_Antibiotic_Gudidelines_2015.pdf

[x] Ceftriaxone, IV: Workowski KA, Bolan GA; Centers for Disease Control and Prevention. Sexually transmitted diseases treatment guidelines, 2015. MMWR Recomm Rep. 2015 Jun 5;64(RR-03):1-137. Erratum in: MMWR Recomm Rep. 2015 Aug 28;64(33):924. https://www.ncbi.nlm.nih.gov/pubmed/26042815

Azithromycin, oral: Workowski KA, Bolan GA; Centers for Disease Control and Prevention. Sexually transmitted diseases treatment guidelines, 2015. MMWR Recomm Rep. 2015 Jun 5;64(RR-03):1-137. Erratum in: MMWR Recomm Rep. 2015 Aug 28;64(33):924. https://www.ncbi.nlm.nih.gov/pubmed/26042815

[xi] NSAIDs as a therapeutic class (diclofenac, naproxen, ibuprofen): Affordable Medicines, EDP-Adult Hospital level. NSAIDs – comparative review of efficacy and safety, 15 January2018. http://www.health.gov.za

NSAIDs as a therapeutic class (diclofenac, naproxen, ibuprofen): Van Walsem A, Pandhi S, Nixon RM, Guyot P, Karabis A, Moore RA. Relative benefit-risk comparing diclofenac to other traditional non-steroidal anti-inflammatory drugs and cyclooxygenase-2 inhibitors in patients with osteoarthritis or rheumatoid arthritis: a network meta-analysis. Arthritis Research & Therapy 2015;17:66. https://www.ncbi.nlm.nih.gov/pubmed/25879879

NSAIDs as a therapeutic class (diclofenac, naproxen, ibuprofen): Nissen SE, Yeomans ND, Solomon DH, Lüscher TF, et al. Cardiovascular Safety of Celecoxib, Naproxen, or Ibuprofen for Arthritis. N Engl J Med 2016;375:2519-29. https://www.ncbi.nlm.nih.gov/pubmed/28379793

NSAIDs as a therapeutic class (diclofenac, naproxen, ibuprofen): Coxib and traditional NSAID Trialists' (CNT) Collaboration. Vascular and upper gastrointestinal effects of non-steroidal anti-inflammatory drugs: meta-analyses of individual participant data from randomised trials. Lancet 2013; 382: 769–79. https://www.ncbi.nlm.nih.gov/pubmed/23726390

NSAIDs as a therapeutic class (diclofenac, naproxen, ibuprofen): Trelle S, Reichenbach S, Wandel S, Hildebrand P, Tschannen B, et al. Cardiovascular safety of non-steroidal anti-inflammatory drugs: network meta-analysis. BMJ 2011;342:c7086. https://www.ncbi.nlm.nih.gov/pubmed/21224324

NSAIDs as a therapeutic class (diclofenac, naproxen, ibuprofen): Ong CKS, Lirk P, Tan Ch, Seymour RA. An evidence-based update on nonsteroidal anti-inflammatory drugs. Clinical Medicine and Research 2007; 5(1):19-34. https://www.ncbi.nlm.nih.gov/pubmed/17456832

NSAIDs as a therapeutic class (diclofenac, naproxen, ibuprofen): Stam WB, Jansen JP, Taylor SD. Efficacy of etoricoxib, lumiracoxib, non-selective NSAIDs, and acetaminophen in osteoarthritis: a mixed treatment comparison. The Open Rheumatology Journal 2012; 6:6-20. https://www.ncbi.nlm.nih.gov/pubmed/22582102

NSAIDs as a therapeutic class (diclofenac, naproxen, ibuprofen): Bello AE, Holt RJ. Cardiovascular risk with non-steroidal anti-inflammatory drugs: clinical implications. Drug Saf. 2014 Nov;37(11):897-902. https://www.ncbi.nlm.nih.gov/pubmed/25079141

NSAIDs as a therapeutic class (diclofenac, naproxen, ibuprofen): South African Medicines Formulary. 12th Edition. Division of Clinical Pharmacology. University of Cape Town, 2016.

[xii] NSAIDs as a therapeutic class (diclofenac, naproxen, ibuprofen): Affordable Medicines, EDP-Adult Hospital level. NSAIDs – comparative review of efficacy and safety, 15 January2018. http://www.health.gov.za

NSAIDs as a therapeutic class (diclofenac, naproxen, ibuprofen): Van Walsem A, Pandhi S, Nixon RM, Guyot P, Karabis A, Moore RA. Relative benefit-risk comparing diclofenac to other traditional non-steroidal anti-inflammatory drugs and cyclooxygenase-2 inhibitors in patients with osteoarthritis or rheumatoid arthritis: a network meta-analysis. Arthritis Research & Therapy 2015;17:66. https://www.ncbi.nlm.nih.gov/pubmed/25879879

NSAIDs as a therapeutic class (diclofenac, naproxen, ibuprofen): Nissen SE, Yeomans ND, Solomon DH, Lüscher TF, et al. Cardiovascular Safety of Celecoxib, Naproxen, or Ibuprofen for Arthritis. N Engl J Med 2016;375:2519-29. https://www.ncbi.nlm.nih.gov/pubmed/28379793

NSAIDs as a therapeutic class (diclofenac, naproxen, ibuprofen): Coxib and traditional NSAID Trialists' (CNT) Collaboration. Vascular and upper gastrointestinal effects of non-steroidal anti-inflammatory drugs: meta-analyses of individual participant data from randomised trials. Lancet 2013; 382: 769–79. https://www.ncbi.nlm.nih.gov/pubmed/23726390

NSAIDs as a therapeutic class (diclofenac, naproxen, ibuprofen): Trelle S, Reichenbach S, Wandel S, Hildebrand P, Tschannen B, et al. Cardiovascular safety of non-steroidal anti-inflammatory drugs: network meta-analysis. BMJ 2011;342:c7086. https://www.ncbi.nlm.nih.gov/pubmed/21224324

NSAIDs as a therapeutic class (diclofenac, naproxen, ibuprofen): Ong CKS, Lirk P, Tan Ch, Seymour RA. An evidence-based update on nonsteroidal anti-inflammatory drugs. Clinical Medicine and Research 2007; 5(1):19-34. https://www.ncbi.nlm.nih.gov/pubmed/17456832

NSAIDs as a therapeutic class (diclofenac, naproxen, ibuprofen): Stam WB, Jansen JP, Taylor SD. Efficacy of etoricoxib, lumiracoxib, non-selective NSAIDs, and acetaminophen in osteoarthritis: a mixed treatment comparison. The Open Rheumatology Journal 2012; 6:6-20. https://www.ncbi.nlm.nih.gov/pubmed/22582102

NSAIDs as a therapeutic class (diclofenac, naproxen, ibuprofen): Bello AE, Holt RJ. Cardiovascular risk with non-steroidal anti-inflammatory drugs: clinical implications. Drug Saf. 2014 Nov;37(11):897-902. https://www.ncbi.nlm.nih.gov/pubmed/25079141

NSAIDs as a therapeutic class (diclofenac, naproxen, ibuprofen): South African Medicines Formulary. 12th Edition. Division of Clinical Pharmacology. University of Cape Town, 2016.

[xiii] Ibuprofen-aspirin interaction: Gladding PA, Webster MW, Farrell HB, Zeng IS, Park R, Ruijne N. The antiplatelet effect of six non-steroidal anti-inflammatory drugs and their pharmacodynamic interaction with aspirin in healthy volunteers. Am J Cardiol. 2008 Apr 1;101(7).http://www.ncbi.nlm.nih.gov/pubmed/18359332

Ibuprofen-aspirin interaction: Meek IL, Vonkeman HE, Kasemier J, Movig KL, van de Laar MA. Interference of NSAIDs with the thrombocyte inhibitory effect of aspirin: a placebo-controlled, ex vivo, serial placebo-controlled serial crossover study. Eur J Clin Pharmacol. 2013 Mar;69(3):365-71. http://www.ncbi.nlm.nih.gov/pubmed/22890587

[xiv] PPI (high risk patients on chronic NSAID therapy): McQuaid KR ,Laine L . Systemic review and meta-analysis of adverse events of low-dose aspirin and clopidogrel in randomized controlled trials. Am J Med 2006;119:624–38. http://www.ncbi.nlm.nih.gov/pubmed/16887404

PPI (high risk patients on chronic NSAID therapy): Serrano P, Lanas A, Arroyo MT, Ferreira IJ. Risk of upper gastrointestinal bleeding in patients taking low-dose aspirin for the prevention of cardiovascular diseases. Aliment PharmacolTher. 2002 Nov;16(11):1945-53. http://www.ncbi.nlm.nih.gov/pubmed/12390104

PPI (high risk patients on chronic NSAID therapy): Lanza FL, Chan FK, Quigley EM; Practice Parameters Committee of the American College of Gastroenterology. Guidelines for prevention of NSAID-related ulcer complications. Am J Gastroenterol. 2009 Mar;104(3):728-38. http://www.ncbi.nlm.nih.gov/pubmed/19240698

PPI (high risk patients on chronic NSAID therapy): Narum S, Westergren T, Klemp M. Corticosteroids and risk of gastrointestinal bleeding: a systematic review and meta-analysis. BMJ Open. 2014 May15;4(5):e004587. https://www.ncbi.nlm.nih.gov/pubmed/24833682

PPI (high risk patients on chronic NSAID therapy): Scarpignato C, Gatta L, Zullo A, Blandizzi C; SIF-AIGO-FIMMG Group; Italian Society of Pharmacology, the Italian Association of Hospital Gastroenterologists, and the Italian Federation of General Practitioners. Effective and safe proton pump inhibitor therapy in acid-related diseases - A position paper addressing benefits and potential harms of acid suppression. BMC Med. 2016 Nov 9;14(1):179. https://www.ncbi.nlm.nih.gov/pubmed/27825371

[xv] Intra-articular corticosteroids: South African Medicines Formulary. 12th Edition. Division of Clinical Pharmacology. University of Cape Town, 2016.

[xvi] Management of gout: Dalbeth N, Reid S, Stamp LK, Arroll B. Making the right thing the easy thing to do: strategies to improve outcomes in gout. Lancet Rheumatology. October 01, 2019. 1:2:PE122-E131. DOI: https://doi.org/10.1016/S2665-9913(19)30004-9

[xvii] NSAIDs as a therapeutic class (diclofenac, naproxen, ibuprofen): Affordable Medicines, EDP-Adult Hospital level. NSAIDs – comparative review of efficacy and safety, 15 January2018. http://www.health.gov.za

NSAIDs as a therapeutic class (diclofenac, naproxen, ibuprofen): Van Walsem A, Pandhi S, Nixon RM, Guyot P, Karabis A, Moore RA. Relative benefit-risk comparing diclofenac to other traditional non-steroidal anti-inflammatory drugs and cyclooxygenase-2 inhibitors in patients with osteoarthritis or rheumatoid arthritis: a network meta-analysis. Arthritis Research & Therapy 2015;17:66. https://www.ncbi.nlm.nih.gov/pubmed/25879879

NSAIDs as a therapeutic class (diclofenac, naproxen, ibuprofen): Nissen SE, Yeomans ND, Solomon DH, Lüscher TF, et al. Cardiovascular Safety of Celecoxib, Naproxen, or Ibuprofen for Arthritis. N Engl J Med 2016;375:2519-29. https://www.ncbi.nlm.nih.gov/pubmed/28379793

NSAIDs as a therapeutic class (diclofenac, naproxen, ibuprofen): Coxib and traditional NSAID Trialists' (CNT) Collaboration. Vascular and upper gastrointestinal effects of non-steroidal anti-inflammatory drugs: meta-analyses of individual participant data from randomised trials. Lancet 2013; 382: 769–79.

https://www.ncbi.nlm.nih.gov/pubmed/23726390

NSAIDs as a therapeutic class (diclofenac, naproxen, ibuprofen): Trelle S, Reichenbach S, Wandel S, Hildebrand P, Tschannen B, et al. Cardiovascular safety of non-steroidal anti-inflammatory drugs: network meta-analysis. BMJ 2011;342:c7086. https://www.ncbi.nlm.nih.gov/pubmed/21224324

NSAIDs as a therapeutic class (diclofenac, naproxen, ibuprofen): Ong CKS, Lirk P, Tan Ch, Seymour RA. An evidence-based update on nonsteroidal anti-inflammatory drugs. Clinical Medicine and Research 2007; 5(1):19-34. https://www.ncbi.nlm.nih.gov/pubmed/17456832

NSAIDs as a therapeutic class (diclofenac, naproxen, ibuprofen): Stam WB, Jansen JP, Taylor SD. Efficacy of etoricoxib, lumiracoxib, non-selective NSAIDs, and acetaminophen in osteoarthritis: a mixed treatment comparison. The Open Rheumatology Journal 2012; 6:6-20. https://www.ncbi.nlm.nih.gov/pubmed/22582102

NSAIDs as a therapeutic class (diclofenac, naproxen, ibuprofen): Bello AE, Holt RJ. Cardiovascular risk with non-steroidal anti-inflammatory drugs: clinical implications. Drug Saf. 2014 Nov;37(11):897-902. https://www.ncbi.nlm.nih.gov/pubmed/25079141

NSAIDs as a therapeutic class (diclofenac, naproxen, ibuprofen): South African Medicines Formulary. 12th Edition. Division of Clinical Pharmacology. University of Cape Town, 2016.

[xviii] PPI (high risk patients on chronic NSAID therapy): McQuaid KR ,Laine L . Systemic review and meta-analysis of adverse events of low-dose aspirin and clopidogrel in randomized controlled trials. Am J Med 2006;119:624–38. http://www.ncbi.nlm.nih.gov/pubmed/16887404

PPI (high risk patients on chronic NSAID therapy): Serrano P, Lanas A, Arroyo MT, Ferreira IJ. Risk of upper gastrointestinal bleeding in patients taking low-dose aspirin for the prevention of cardiovascular diseases. Aliment PharmacolTher. 2002 Nov;16(11):1945-53. http://www.ncbi.nlm.nih.gov/pubmed/12390104

PPI (high risk patients on chronic NSAID therapy): Lanza FL, Chan FK, Quigley EM; Practice Parameters Committee of the American College of Gastroenterology. Guidelines for prevention of NSAID-related ulcer complications. Am J Gastroenterol. 2009 Mar;104(3):728-38. http://www.ncbi.nlm.nih.gov/pubmed/19240698

PPI (high risk patients on chronic NSAID therapy): Narum S, Westergren T, Klemp M. Corticosteroids and risk of gastrointestinal bleeding: a systematic review and meta-analysis. BMJ Open. 2014 May15;4(5):e004587. https://www.ncbi.nlm.nih.gov/pubmed/24833682

PPI (high risk patients on chronic NSAID therapy): Scarpignato C, Gatta L, Zullo A, Blandizzi C; SIF-AIGO-FIMMG Group; Italian Society of Pharmacology, the Italian Association of Hospital Gastroenterologists, and the Italian Federation of General Practitioners. Effective and safe proton pump inhibitor therapy in acid-related diseases - A position paper addressing benefits and potential harms of acid suppression. BMC Med. 2016 Nov 9;14(1):179. https://www.ncbi.nlm.nih.gov/pubmed/27825371

[xix] Allopurinol, oral – maximum dose: South African Medicines Formulary. 12th Edition. Division of Clinical Pharmacology. University of Cape Town, 2016.

[xx] Allopurinol, oral – renal adjusted dosing: Siu YP, Leung KT, Tong MK, Kwan TH. Use of allopurinol in slowing the progression of renal disease through its ability to lower serum uric acid level. Am J Kidney Dis. 2006;47(1):51–59. https://www.ncbi.nlm.nih.gov/pubmed/16377385

Allopurinol, oral – renal adjusted dosing: Goicoechea M, de Vinuesa SG, Verdalles U, Ruiz-Caro C, Ampuero J, Rincón A, Arroyo D, Luño J. Effect of allopurinol in chronic kidney disease progression and cardiovascular risk. Clin J Am Soc Nephrol. 2010 Aug;5(8):1388-93. https://www.ncbi.nlm.nih.gov/pubmed/20538833

Allopurinol, oral – renal adjusted dosing: South African Medicines Formulary. 12th Edition. Division of Clinical Pharmacology. University of Cape Town, 2016.

Allopurinol, oral – renal adjusted dosing: Bennet et al. Drug Prescribing in Renal Failure. 5th Edition. Philadelphia: American College of Physicians. 2007;104.

[xxi] Allopurinol, oral: hypersensitivity caution: Yang CY, Chen CH, Deng ST, Huang CS, Lin YJ, Chen YJ, Wu CY, Hung SI, Chung WH. Allopurinol Use and Risk of Fatal Hypersensitivity Reactions: A Nationwide Population-Based Study in Taiwan. JAMA Intern Med. 2015 Sep;175(9):1550-7. https://www.ncbi.nlm.nih.gov/pubmed/26193384

[xxii] NSAIDs as a therapeutic class (diclofenac, naproxen, ibuprofen): Affordable Medicines, EDP-Adult Hospital level. NSAIDs – comparative review of efficacy and safety, 15 January2018. http://www.health.gov.za

NSAIDs as a therapeutic class (diclofenac, naproxen, ibuprofen): Van Walsem A, Pandhi S, Nixon RM, Guyot P, Karabis A, Moore RA. Relative benefit-risk comparing diclofenac to other traditional non-steroidal anti-inflammatory drugs and cyclooxygenase-2 inhibitors in patients with osteoarthritis or rheumatoid arthritis: a network meta-analysis. Arthritis Research & Therapy 2015;17:66. https://www.ncbi.nlm.nih.gov/pubmed/25879879

NSAIDs as a therapeutic class (diclofenac, naproxen, ibuprofen): Nissen SE, Yeomans ND, Solomon DH, Lüscher TF, et al. Cardiovascular Safety of Celecoxib, Naproxen, or Ibuprofen for Arthritis. N Engl J Med 2016;375:2519-29. https://www.ncbi.nlm.nih.gov/pubmed/28379793

NSAIDs as a therapeutic class (diclofenac, naproxen, ibuprofen): Coxib and traditional NSAID Trialists' (CNT) Collaboration. Vascular and upper gastrointestinal effects of non-steroidal anti-inflammatory drugs: meta-analyses of individual participant data from randomised trials. Lancet 2013; 382: 769–79. https://www.ncbi.nlm.nih.gov/pubmed/23726390

NSAIDs as a therapeutic class (diclofenac, naproxen, ibuprofen): Trelle S, Reichenbach S, Wandel S, Hildebrand P, Tschannen B, et al. Cardiovascular safety of non-steroidal anti-inflammatory drugs: network meta-analysis. BMJ 2011;342:c7086. https://www.ncbi.nlm.nih.gov/pubmed/21224324

NSAIDs as a therapeutic class (diclofenac, naproxen, ibuprofen): Ong CKS, Lirk P, Tan Ch, Seymour RA. An evidence-based update on nonsteroidal anti-inflammatory drugs. Clinical Medicine and Research 2007; 5(1):19-34. https://www.ncbi.nlm.nih.gov/pubmed/17456832

NSAIDs as a therapeutic class (diclofenac, naproxen, ibuprofen): Stam WB, Jansen JP, Taylor SD. Efficacy of etoricoxib, lumiracoxib, non-selective NSAIDs, and acetaminophen in osteoarthritis: a mixed treatment comparison.

The Open Rheumatology Journal 2012; 6:6-20. https://www.ncbi.nlm.nih.gov/pubmed/22582102

NSAIDs as a therapeutic class (diclofenac, naproxen, ibuprofen): Bello AE, Holt RJ. Cardiovascular risk with non-steroidal anti-inflammatory drugs: clinical implications. Drug Saf. 2014 Nov;37(11):897-902. https://www.ncbi.nlm.nih.gov/pubmed/25079141

NSAIDs as a therapeutic class (diclofenac, naproxen, ibuprofen): South African Medicines Formulary. 12th Edition. Division of Clinical Pharmacology. University of Cape Town, 2016.

[xxiii] Colchicine – prophylaxis for breakthrough gout attacks: Wortmann RL, Macdonald PA, Hunt B, Jackson RL. Effect of prophylaxis on gout flares after the initiation of urate-lowering therapy: analysis of data from three phase III trials. Clin Ther. 2010 Dec;32(14):2386-97. https://www.ncbi.nlm.nih.gov/pubmed/21353107

[xxiv] PPI (high risk patients on chronic NSAID therapy): McQuaid KR ,Laine L . Systemic review and meta-analysis of adverse events of low-dose aspirin and clopidogrel in randomized controlled trials. Am J Med 2006;119:624–38. http://www.ncbi.nlm.nih.gov/pubmed/16887404

PPI (high risk patients on chronic NSAID therapy): Serrano P, Lanas A, Arroyo MT, Ferreira IJ. Risk of upper gastrointestinal bleeding in patients taking low-dose aspirin for the prevention of cardiovascular diseases. Aliment PharmacolTher. 2002 Nov;16(11):1945-53. http://www.ncbi.nlm.nih.gov/pubmed/12390104

PPI (high risk patients on chronic NSAID therapy): Lanza FL, Chan FK, Quigley EM; Practice Parameters Committee of the American College of Gastroenterology. Guidelines for prevention of NSAID-related ulcer complications. Am J Gastroenterol. 2009 Mar;104(3):728-38. http://www.ncbi.nlm.nih.gov/pubmed/19240698

PPI (high risk patients on chronic NSAID therapy): Narum S, Westergren T, Klemp M. Corticosteroids and risk of gastrointestinal bleeding: a systematic review and meta-analysis. BMJ Open. 2014 May15;4(5):e004587. https://www.ncbi.nlm.nih.gov/pubmed/24833682

PPI (high risk patients on chronic NSAID therapy): Scarpignato C, Gatta L, Zullo A, Blandizzi C; SIF-AIGO-FIMMG Group; Italian Society of Pharmacology, the Italian Association of Hospital Gastroenterologists, and the Italian Federation of General Practitioners. Effective and safe proton pump inhibitor therapy in acid-related diseases - A position paper addressing benefits and potential harms of acid suppression. BMC Med. 2016 Nov 9;14(1):179. https://www.ncbi.nlm.nih.gov/pubmed/27825371

[xxv] NSAIDs as a therapeutic class (diclofenac, naproxen, ibuprofen): Affordable Medicines, EDP-Adult Hospital level. NSAIDs – comparative review of efficacy and safety, 15 January2018. http://www.health.gov.za

NSAIDs as a therapeutic class (diclofenac, naproxen, ibuprofen): Van Walsem A, Pandhi S, Nixon RM, Guyot P, Karabis A, Moore RA. Relative benefit-risk comparing diclofenac to other traditional non-steroidal anti-inflammatory drugs and cyclooxygenase-2 inhibitors in patients with osteoarthritis or rheumatoid arthritis: a network meta-analysis. Arthritis Research & Therapy 2015;17:66. https://www.ncbi.nlm.nih.gov/pubmed/25879879

NSAIDs as a therapeutic class (diclofenac, naproxen, ibuprofen): Nissen SE, Yeomans ND, Solomon DH, Lüscher TF, et al. Cardiovascular Safety of Celecoxib, Naproxen, or Ibuprofen for Arthritis. N Engl J Med 2016;375:2519-29. https://www.ncbi.nlm.nih.gov/pubmed/28379793

NSAIDs as a therapeutic class (diclofenac, naproxen, ibuprofen): Coxib and traditional NSAID Trialists' (CNT) Collaboration. Vascular and upper gastrointestinal effects of non-steroidal anti-inflammatory drugs: meta-analyses of individual participant data from randomised trials. Lancet 2013; 382: 769–79. https://www.ncbi.nlm.nih.gov/pubmed/23726390

NSAIDs as a therapeutic class (diclofenac, naproxen, ibuprofen): Trelle S, Reichenbach S, Wandel S, Hildebrand P, Tschannen B, et al. Cardiovascular safety of non-steroidal anti-inflammatory drugs: network meta-analysis. BMJ 2011;342:c7086. https://www.ncbi.nlm.nih.gov/pubmed/21224324

NSAIDs as a therapeutic class (diclofenac, naproxen, ibuprofen): Ong CKS, Lirk P, Tan Ch, Seymour RA. An evidence-based update on nonsteroidal anti-inflammatory drugs. Clinical Medicine and Research 2007; 5(1):19-34. https://www.ncbi.nlm.nih.gov/pubmed/17456832

NSAIDs as a therapeutic class (diclofenac, naproxen, ibuprofen): Stam WB, Jansen JP, Taylor SD. Efficacy of etoricoxib, lumiracoxib, non-selective NSAIDs, and acetaminophen in osteoarthritis: a mixed treatment comparison. The Open Rheumatology Journal 2012; 6:6-20. https://www.ncbi.nlm.nih.gov/pubmed/22582102

NSAIDs as a therapeutic class (diclofenac, naproxen, ibuprofen): Bello AE, Holt RJ. Cardiovascular risk with non-steroidal anti-inflammatory drugs: clinical implications. Drug Saf. 2014 Nov;37(11):897-902. https://www.ncbi.nlm.nih.gov/pubmed/25079141

NSAIDs as a therapeutic class (diclofenac, naproxen, ibuprofen): South African Medicines Formulary. 12th Edition. Division of Clinical Pharmacology. University of Cape Town, 2016.

[xxvi] PPI (high risk patients on chronic NSAID therapy): McQuaid KR ,Laine L . Systemic review and meta-analysis of adverse events of low-dose aspirin and clopidogrel in randomized controlled trials. Am J Med 2006;119:624–38. http://www.ncbi.nlm.nih.gov/pubmed/16887404

PPI (high risk patients on chronic NSAID therapy): Serrano P, Lanas A, Arroyo MT, Ferreira IJ. Risk of upper gastrointestinal bleeding in patients taking low-dose aspirin for the prevention of cardiovascular diseases. Aliment PharmacolTher. 2002 Nov;16(11):1945-53. http://www.ncbi.nlm.nih.gov/pubmed/12390104

PPI (high risk patients on chronic NSAID therapy): Lanza FL, Chan FK, Quigley EM; Practice Parameters Committee of the American College of Gastroenterology. Guidelines for prevention of NSAID-related ulcer complications. Am J Gastroenterol. 2009 Mar;104(3):728-38. http://www.ncbi.nlm.nih.gov/pubmed/19240698

PPI (high risk patients on chronic NSAID therapy): Narum S, Westergren T, Klemp M. Corticosteroids and risk of gastrointestinal bleeding: a systematic review and meta-analysis. BMJ Open. 2014 May15;4(5):e004587. https://www.ncbi.nlm.nih.gov/pubmed/24833682

PPI (high risk patients on chronic NSAID therapy): Scarpignato C, Gatta L, Zullo A, Blandizzi C; SIF-AIGO-FIMMG Group; Italian Society of Pharmacology, the Italian Association of Hospital Gastroenterologists, and the Italian Federation of General Practitioners. Effective and safe proton pump inhibitor therapy in acid-related diseases - A

position paper addressing benefits and potential harms of acid suppression. BMC Med. 2016 Nov 9;14(1):179. https://www.ncbi.nlm.nih.gov/pubmed/27825371

[xxvii] NSAIDs as a therapeutic class (diclofenac, naproxen, ibuprofen): Affordable Medicines, EDP-Adult Hospital level. NSAIDs – comparative review of efficacy and safety, 15 January2018. http://www.health.gov.za

NSAIDs as a therapeutic class (diclofenac, naproxen, ibuprofen): Van Walsem A, Pandhi S, Nixon RM, Guyot P, Karabis A, Moore RA. Relative benefit-risk comparing diclofenac to other traditional non-steroidal anti-inflammatory drugs and cyclooxygenase-2 inhibitors in patients with osteoarthritis or rheumatoid arthritis: a network meta-analysis. Arthritis Research & Therapy 2015;17:66. https://www.ncbi.nlm.nih.gov/pubmed/25879879

NSAIDs as a therapeutic class (diclofenac, naproxen, ibuprofen): Nissen SE, Yeomans ND, Solomon DH, Lüscher TF, et al. Cardiovascular Safety of Celecoxib, Naproxen, or Ibuprofen for Arthritis. N Engl J Med 2016;375:2519-29. https://www.ncbi.nlm.nih.gov/pubmed/28379793

NSAIDs as a therapeutic class (diclofenac, naproxen, ibuprofen): Coxib and traditional NSAID Trialists' (CNT) Collaboration. Vascular and upper gastrointestinal effects of non-steroidal anti-inflammatory drugs: meta-analyses of individual participant data from randomised trials. Lancet 2013; 382: 769–79. https://www.ncbi.nlm.nih.gov/pubmed/23726390

NSAIDs as a therapeutic class (diclofenac, naproxen, ibuprofen): Trelle S, Reichenbach S, Wandel S, Hildebrand P, Tschannen B, et al. Cardiovascular safety of non-steroidal anti-inflammatory drugs: network meta-analysis. BMJ 2011;342:c7086. https://www.ncbi.nlm.nih.gov/pubmed/21224324

NSAIDs as a therapeutic class (diclofenac, naproxen, ibuprofen): Ong CKS, Lirk P, Tan Ch, Seymour RA. An evidence-based update on nonsteroidal anti-inflammatory drugs. Clinical Medicine and Research 2007; 5(1):19-34. https://www.ncbi.nlm.nih.gov/pubmed/17456832

NSAIDs as a therapeutic class (diclofenac, naproxen, ibuprofen): Stam WB, Jansen JP, Taylor SD. Efficacy of etoricoxib, lumiracoxib, non-selective NSAIDs, and acetaminophen in osteoarthritis: a mixed treatment comparison. The Open Rheumatology Journal 2012; 6:6-20. https://www.ncbi.nlm.nih.gov/pubmed/22582102

NSAIDs as a therapeutic class (diclofenac, naproxen, ibuprofen): Bello AE, Holt RJ. Cardiovascular risk with non-steroidal anti-inflammatory drugs: clinical implications. Drug Saf. 2014 Nov;37(11):897-902. https://www.ncbi.nlm.nih.gov/pubmed/25079141

NSAIDs as a therapeutic class (diclofenac, naproxen, ibuprofen): South African Medicines Formulary. 12th Edition. Division of Clinical Pharmacology. University of Cape Town, 2016.

[xxviii] PPI (high risk patients on chronic NSAID therapy): McQuaid KR ,Laine L . Systemic review and meta-analysis of adverse events of low-dose aspirin and clopidogrel in randomized controlled trials. Am J Med 2006;119:624–38. http://www.ncbi.nlm.nih.gov/pubmed/16887404

PPI (high risk patients on chronic NSAID therapy): Serrano P, Lanas A, Arroyo MT, Ferreira IJ. Risk of upper gastrointestinal bleeding in patients taking low-dose aspirin for the prevention of cardiovascular diseases. Aliment PharmacolTher. 2002 Nov;16(11):1945-53. http://www.ncbi.nlm.nih.gov/pubmed/12390104

PPI (high risk patients on chronic NSAID therapy): Lanza FL, Chan FK, Quigley EM; Practice Parameters Committee of the American College of Gastroenterology. Guidelines for prevention of NSAID-related ulcer complications. Am J Gastroenterol. 2009 Mar;104(3):728-38. http://www.ncbi.nlm.nih.gov/pubmed/19240698

PPI (high risk patients on chronic NSAID therapy): Narum S, Westergren T, Klemp M. Corticosteroids and risk of gastrointestinal bleeding: a systematic review and meta-analysis. BMJ Open. 2014 May15;4(5):e004587. https://www.ncbi.nlm.nih.gov/pubmed/24833682

PPI (high risk patients on chronic NSAID therapy): Scarpignato C, Gatta L, Zullo A, Blandizzi C; SIF-AIGO-FIMMG Group; Italian Society of Pharmacology, the Italian Association of Hospital Gastroenterologists, and the Italian Federation of General Practitioners. Effective and safe proton pump inhibitor therapy in acid-related diseases - A position paper addressing benefits and potential harms of acid suppression. BMC Med. 2016 Nov 9;14(1):179. https://www.ncbi.nlm.nih.gov/pubmed/27825371

[xxix] Ceftriaxone, IM: National Department of Health STI Guidelines, 2014 and PHC STGs and EML, 2014. http://www.health.gov.za

Lidocaine 1% with epinephrine (adrenaline): National Department of Health STI Guidelines, 2014 and PHC STGs and EML, 2014. http://www.health.gov.za

Azithromycin: National Department of Health STI Guidelines, 2014 and PHC STGs and EML, 2014. http://www.health.gov.za

[xxx] NSAIDs as a therapeutic class (diclofenac, naproxen, ibuprofen): Affordable Medicines, EDP-Adult Hospital level. NSAIDs – comparative review of efficacy and safety, 15 January2018. http://www.health.gov.za

NSAIDs as a therapeutic class (diclofenac, naproxen, ibuprofen): Van Walsem A, Pandhi S, Nixon RM, Guyot P, Karabis A, Moore RA. Relative benefit-risk comparing diclofenac to other traditional non-steroidal anti-inflammatory drugs and cyclooxygenase-2 inhibitors in patients with osteoarthritis or rheumatoid arthritis: a network meta-analysis. Arthritis Research & Therapy 2015;17:66. https://www.ncbi.nlm.nih.gov/pubmed/25879879

NSAIDs as a therapeutic class (diclofenac, naproxen, ibuprofen): Nissen SE, Yeomans ND, Solomon DH, Lüscher TF, et al. Cardiovascular Safety of Celecoxib, Naproxen, or Ibuprofen for Arthritis. N Engl J Med 2016;375:2519-29. https://www.ncbi.nlm.nih.gov/pubmed/28379793

NSAIDs as a therapeutic class (diclofenac, naproxen, ibuprofen): Coxib and traditional NSAID Trialists' (CNT) Collaboration. Vascular and upper gastrointestinal effects of non-steroidal anti-inflammatory drugs: meta-analyses of individual participant data from randomised trials. Lancet 2013; 382: 769–79. https://www.ncbi.nlm.nih.gov/pubmed/23726390

NSAIDs as a therapeutic class (diclofenac, naproxen, ibuprofen): Trelle S, Reichenbach S, Wandel S, Hildebrand P, Tschannen B, et al. Cardiovascular safety of non-steroidal anti-inflammatory drugs: network meta-analysis. BMJ 2011;342:c7086. https://www.ncbi.nlm.nih.gov/pubmed/21224324

NSAIDs as a therapeutic class (diclofenac, naproxen, ibuprofen): Ong CKS, Lirk P, Tan Ch, Seymour RA. An evidence-based update on nonsteroidal anti-inflammatory drugs. Clinical Medicine and Research 2007; 5(1):19-34. https://www.ncbi.nlm.nih.gov/pubmed/17456832

NSAIDs as a therapeutic class (diclofenac, naproxen, ibuprofen): Stam WB, Jansen JP, Taylor SD. Efficacy of etoricoxib, lumiracoxib, non-selective NSAIDs, and acetaminophen in osteoarthritis: a mixed treatment comparison. The Open Rheumatology Journal 2012; 6:6-20. https://www.ncbi.nlm.nih.gov/pubmed/22582102

NSAIDs as a therapeutic class (diclofenac, naproxen, ibuprofen): Bello AE, Holt RJ. Cardiovascular risk with non-steroidal anti-inflammatory drugs: clinical implications. Drug Saf. 2014 Nov;37(11):897-902. https://www.ncbi.nlm.nih.gov/pubmed/25079141

NSAIDs as a therapeutic class (diclofenac, naproxen, ibuprofen): South African Medicines Formulary. 12th Edition. Division of Clinical Pharmacology. University of Cape Town, 2016.

[xxxi] PPI (high risk patients on chronic NSAID therapy): McQuaid KR ,Laine L . Systemic review and meta-analysis of adverse events of low-dose aspirin and clopidogrel in randomized controlled trials. Am J Med 2006;119:624–38. http://www.ncbi.nlm.nih.gov/pubmed/16887404

PPI (high risk patients on chronic NSAID therapy): Serrano P, Lanas A, Arroyo MT, Ferreira IJ. Risk of upper gastrointestinal bleeding in patients taking low-dose aspirin for the prevention of cardiovascular diseases. Aliment PharmacolTher. 2002 Nov;16(11):1945-53. http://www.ncbi.nlm.nih.gov/pubmed/12390104

PPI (high risk patients on chronic NSAID therapy): Lanza FL, Chan FK, Quigley EM; Practice Parameters Committee of the American College of Gastroenterology. Guidelines for prevention of NSAID-related ulcer complications. Am J Gastroenterol. 2009 Mar;104(3):728-38. http://www.ncbi.nlm.nih.gov/pubmed/19240698

PPI (high risk patients on chronic NSAID therapy): Narum S, Westergren T, Klemp M. Corticosteroids and risk of gastrointestinal bleeding: a systematic review and meta-analysis. BMJ Open. 2014 May15;4(5):e004587. https://www.ncbi.nlm.nih.gov/pubmed/24833682

PPI (high risk patients on chronic NSAID therapy): Scarpignato C, Gatta L, Zullo A, Blandizzi C; SIF-AIGO-FIMMG Group; Italian Society of Pharmacology, the Italian Association of Hospital Gastroenterologists, and the Italian Federation of General Practitioners. Effective and safe proton pump inhibitor therapy in acid-related diseases - A position paper addressing benefits and potential harms of acid suppression. BMC Med. 2016 Nov 9;14(1):179. https://www.ncbi.nlm.nih.gov/pubmed/27825371

[xxxii]Chloroquine: Ruiz-Irastorza G, Ramos-Casals M, Brito-Zeron P, Khamashta MA. Clinical efficacy and side effects of antimalarials in systemic lupus erythematosus: a systematic review. Ann Rheum Dis. 2010 Jan;69(1):20-8.http://www.ncbi.nlm.nih.gov/pubmed/19103632

[xxxiii]Amlodipine: Ennis H, Anderson ME, Wilkinson J, Herrick AL. Calcium channel blockers for primary Raynaud's phenomenon. Cochrane Database Syst Rev. 2014 Jan 30;1:CD002069. http://www.ncbi.nlm.nih.gov/pubmed/24482037

CHAPTER 14

NEUROLOGICAL DISORDERS

14.1 CEREBROVASCULAR DISEASE

14.1.1 STROKE

I61.0-6/I61.8-9/I63.0-6/I63.8-9/I64 + (G46.0-8*)

GENERAL MEASURES

Optimise hydration and nutrition; insert nasogastric tube if patient cannot swallow. Take precautions to ensure an open airway if patient is unconscious. Physiotherapy and good nursing care. Consider rehabilitation for suitable patients and refer if necessary.

Do an ECG to rule out an acute coronary event or atrial fibrillation as precipitants.

Do serology to exclude meningovascular syphilis (in patients <45 years old who do not have risk factors for stroke).

Check lipid profile in ischaemic strokes.

Ischaemic stroke in young adults (< 45 years of age) may be due to atherosclerosis, but also consider:

» Embolic: e.g. rheumatic heart disease, atrial fibrillation, cardiomyopathy, previous myocardial infarction, and, very rarely, patent foramen ovale: history, careful clinical cardiac examination, ECG/CXR, and echocardiography.
» Vessel wall disease: e.g. syphilis, HIV infection, collagen-vascular diseases, TB or bacterial meningitis, and extracranial arterial dissection. Investigate as guided by clinical presentation, but at least perform syphilis and HIV serology, urinalysis (haematuria and/or proteinuria), and ANF/RF. ANCA, and cerebral angiography or carotid Doppler may be indicated. Note that absence of a carotid bruit does not exclude significant carotid stenosis.
» Hypercoagulable states: e.g. antiphospholipid antibody syndrome, thrombotic thrombocytopenic purpura. Useful screening investigations are FBC and, in women, PTT/Anti-phospholipid Ab. Testing and management of thrombophilias should be done in consultation with an expert.

Initiate a palliative care approach if the patient's condition is deteriorating / in case of a massive stroke (See Chapter 24: Medicines Used in Palliative Care).

Ensure adequacy of swallowing ability by dietician or by asking the patient to swallow 10 mL of water.

MEDICINE TREATMENT

Hyper-acute management:

Symptom onset ≤ 3 hours:

» Do not give aspirin.
» Refer immediately to hospital that **can provide thrombolytic therapy:**

- Alteplase, IV, 0.9 mg/kg. Total dose should not exceed 90 mg.

- 10 % of total dose given as a bolus and the remainder continued as an infusion over an hour.

LoE:Ib[i]

Symptoms >3 hours:

LoE:Ia[ii]

- Aspirin, oral, 300 mg, immediately.

Followed by:

- Aspirin, oral, 150 mg daily.
  - If patient is unable to swallow, administer through a naso-gastric tube.

Do not administer aspirin if there are symptoms suggestive of a sub-arachnoid bleed, e.g. headache, stiff neck, etc.

AND

For DVT prophylaxis, see Section2.8: Venous thrombo-embolism.
Treat secondary pulmonary and urinary tract infections appropriately.

Secondary prevention:

Measures for secondary prevention may not be appropriate for patients with severe disability.

All patients with a thrombotic stroke, not on anticoagulation and irrespective of the LDL level:

- Aspirin, oral, 150 mg daily.

LoE:Ia[iii]

AND

- HMGCoA reductase inhibitors (statins), e.g.:
- Simvastatin, oral, 40 mg at night.

LoE:IIb[iv]

Patients on protease inhibitor:

- Atorvastatin, oral, 10 mg at night.

LoE:IIb[v]

Patients on amlodipine (and not on a protease inhibitor):

- Simvastatin, oral, 10 mg at night.

If patient complains of muscle pain:

LoE:IVb[vi]

Reduce dose:

- HMGCoA reductase inhibitors (statins), e.g.:
- Simvastatin, oral, 10 mg at night.

OR

Consult specialist for further management.

LoE:IVb[vii]

Anticoagulation:

In patients with cardioembolic strokes (e.g. secondary to atrial fibrillation) with no evidence of haemorrhage on CT scan, the optimal time to start anticoagulation therapy is likely to vary among individual patients; this can be from 7 to 14 days and up to 21 days and is dependent on the infarct size (> 1/3 of the hemisphere) and the patient's risk factors for recurrent events.

LoE:IIIb[viii]

Bridging anticoagulation with heparin, or earlier initiation of warfarin, is not recommended because, although it reduces ischaemic stroke recurrence, it increases symptomatic intracranial haemorrhage. LoE:IVb

Blood pressure management:
A transient increase in BP is common after an acute stroke. Lowering BP during the acute phase of stroke (within 6 hours of onset) may not improve morbidity.

Do not actively lower a systolic BP < 220 mm Hg or diastolic BP < 120 mm Hg in the first few days after stroke as this may be associated with an increased risk of death.

In patients presenting with stroke and BP > 220/120 mmHg, lower BP to about 180/110 mm Hg in the first 24 hours.

Antihypertensive medicines may be withheld until patients have suitable oral or enteral access. Cautious incremental reintroduction of treatment is advised to achieve long-term standard BP control. See Section: 3.6.3 Hypertensive crisis, hypertensive emergency.

If BP > 220/120 mm Hg: LoE:IIb[ix]
- Long-acting calcium channel blocker, e.g.:
- Amlodipine, oral, 5 mg daily.

OR

If adequate fluid intake can be ensured: LoE:IIb[x]
- Hydrochlorothiazide, oral, 12.5 mg daily. LoE:IVb

Note:
» There is some evidence of harm from BP reduction within 7 days of acute stroke; after 7 days cautious incremental re-introduction of treatment is advised to achieve long term standard BP control.
» Antihypertensive medicines should be stopped in acute stroke unless the BP is > 220/120 mm Hg (see above). LoE:IIb[xi]
» Reassess the need for re-initiation of patients' previous antihypertensive medication. See Section3.6: Hypertension. LoE:IIb[xii]

REFERRAL

Patients with aspirin intolerance
To a facility with a CT scan:
» Patients with atypical clinical presentation.
» Selected patients with suspected ischaemic stroke who may benefit from thrombolysis with tissue plasminogen activator if initiated within 3 hours of onset of symptoms.
» Patients with suspected posterior cerebral fossa haemorrhage who may require surgical decompression.

» If there is a history suggestive of subarachnoid haemorrhage or if there is neck stiffness.

14.1.2 TRANSIENT ISCHAEMIC ATTACK (TIA)

G45.0-4/G45.8-9

DESCRIPTION

A transient ischaemic attack is an episode of brain, spinal cord, or retinal ischaemia causing focal neurological dysfunction usually for less than one hour. Risk of subsequent stroke is highest in the week after a TIA. Consider hypoglycaemia, epilepsy, and migraine as alternative causes for the symptoms.

Feature	Points
Age ≥60 years	1
BP ≥ 140/90 mmHg	1
Clinical features:	
speech disturbance without weakness OR	1
unilateral weakness	2
Diabetes	1
Duration:	
10 to 59 minutes	1
≥ 1 hour	2

Table 14.1: The $ABCD^2$ scoring system

Reference: Johnston SC, Rothwell PM, Nguyen-Huynh MN, Giles MF, Elkins JS, Bernstein AL, Sidney S. Validation and refinement of scores to predict very early stroke risk after transient ischaemic attack. Lancet. 2007 Jan 27;369(9558):283-92. doi: 10.1016/S0140-6736(07)60150-0. PMID: 17258668.

$ABCD^2$ score ≥ 4 is regarded as high risk and warrants urgent investigation and management as the risk of stroke within the next week is ≥ 4%.

MEDICINE TREATMENT

Cardioembolic disease:

- Warfarin, oral, 5 mg daily.
  - Measure INR after 48 hours, then every 1 to 2 days until within the therapeutic range of 2 to 3 (refer to initiation dosing tables in Appendix II).
  - Adjust dose to keep INR within therapeutic range (refer to Maintenance dosing tables in the Appendix II).

LoE:IVb[xiii]

Other patients:

LoE:IIIb[xiv]

- Aspirin, oral, 150 mg daily.

Lipid control (all patients):

- HMGCoA reductase inhibitors (statins), e.g.:

LoE:IIb[xv]

- Simvastatin, oral, 40 mg at night.

Patients on protease inhibitor:

- Atorvastatin, oral, 10 mg at night. *LoE:IIb*[xvi]

Patients on amlodipine (and not on a protease inhibitor):

- Simvastatin, oral, 10 mg at night. *LoE:IVb*[xvii]

If patient complains of muscle pain:
Reduce dose:

- HMGCoA reductase inhibitors (statins), e.g.:
- Simvastatin, oral, 10 mg at night.

OR

Consult specialist for further management. *LoE:IVb*[xviii]

Manage hypertension – see Section3.6: Hypertension.

14.1.3 SUBARACHNOID HAEMORRHAGE

I60.0-9

DESCRIPTION

Bleeding into the subarachnoid space, most commonly due to the rupture of a vascular aneurysm. Patients typically present with an acute onset of severe headache and may have additional neurological symptoms and signs. Diagnosis is confirmed preferably by neurological imaging and, when this is not available, by demonstrating CSF xanthochromia on lumbar puncture.

GENERAL MEASURES

Maintain normal hydration and electrolyte status.
Control blood pressure.

MEDICINE TREATMENT

Analgesia if level of consciousness is not impaired:
Avoid NSAIDs.

- Paracetamol, oral, 500 mg to1 g, 4 to 6 hourly as required (to a maximum of 4 g in 24 hours).
    - Maximum dose: 15 mg/kg/dose.

If no response to paracetamol:

- Morphine, IV, to a total maximum dose of 10 mg (see Appendix II, for individual dosing and monitoring for response and toxicity).

In all patients presenting with aneurysmal subarachnoid haemorrhage while waiting for transfer to neurosurgical facility and in consultation with neurosurgeon:

- Nimodipine, oral, 60 mg 4 hourly for 21 days.

REFERRAL

All patients with minimal impairment of consciousness level for angiography and appropriate neurosurgical management. Patients initially deemed unsuitable for further investigation, may be referred at a later stage, should their condition improve.

14.2 DEMENTIA

E51.2/E52/E63.9/F00.0-2/F00.9/F01.0-3/F01.8-9/F03

DESCRIPTION

Progressive loss of cognitive function, usually of insidious onset. Initial presentation may be with mild personality or memory changes, before more pronounced defects become evident. Investigate patients for potentially reversible causes:

» Metabolic:
  - Hypothyroidism.
  - Vitamin B_{12} deficiency.
  - Pellagra.
  - Thiamine deficiency (Wernicke's syndrome).
» Medications and drugs:
  - Alcohol abuse.
  - Many medicines with CNS side-effects.
» Infections:
  - Syphilis.
  - HIV.
» Surgical:
  - Chronic subdural haematoma.
  - Normal pressure hydrocephalus.
» Severe depression (may mimic dementia).

Conditions which may worsen already existing dementia include:

» electrolyte disturbances and dehydration.
» infections.
» medicine toxicity.

GENERAL MEASURES

Appropriate care and support, according to the level of impairment.
Ambulatory care is preferred to hospitalisation, if feasible.
Family counselling and support.
Use a palliative care approach: involve a multidisciplinary care team early and plan for advanced dementia care.

MEDICINE TREATMENT

Management is mainly symptomatic.

<u>To control restless patients:</u>

- Haloperidol, oral, 0.75–1.5 mg 8 hourly with a higher dose at night, if required.

Note:
» There is uncertainty of benefit versus harm of long-term use of antipsychotics in dementia, but antipsychotics may be of benefit in severe behavioural and psychological symptoms.
» Inform the family of a possible elevated risk of mortality with prolonged use of antipsychotics.
» If there is no improvement, stop the antipsychotic.
» Initiate treatment at a low dose and titrate to the lowest effective dose for the shortest possible time. Reassess the person at least every 6 weeks, to check whether they still need medication.

LoE:IIIa[xix]

For pellagra:
- Nicotinamide, oral, 100 mg 8 hourly.

Wernicke's syndrome: E51.2 + (F02.8*)
- Thiamine, IM, 500 mg immediately and daily for 3 to 5 days.
  - Follow with thiamine, oral, 100 mg 8 hourly.

CAUTION
Thiamine should preferably be administered prior to intravenous glucose to prevent permanent neurological damage.
Do not delay the dextrose administration in a hypoglycaemic patient.

Prophylaxis in patients at risk (alcoholism, malnutrition): Z29.2
- Thiamine, IM, 200 mg daily or oral, 100 mg 8 hourly for 14 days.

LoE:IIb[xx]

Treat other commonly associated nutritional deficiencies:
If confirmed Vitamin B_{12} deficiency, manage as Section2.1.2: Anaemia, megaloblastic.

14.3 DELIRIUM
See Section20.8: Delirium with perceptual disturbances.

14.4 EPILEPTIC SEIZURES
G40.6-7; G41; R56.8

DESCRIPTION
An epileptic seizure is a change in movement, attention or level of awareness that is sustained or repetitive and occurs because of abnormal and excessive neuronal discharge within the brain.

LoE:IVb[xxi]

Epileptic seizures should be differentiated from:
» Collapse, e.g. syncope; anoxic seizures; transient ischaemic attack; cardiac arrhythmias.
» Movement disorders, e.g. paroxysmal dyskinesias; tic disorders.

» Mental health conditions, e.g., functional/dissociative seizures (also called psychogenic non-epileptic seizures); rage reactions; panic attacks; daydreaming/ inattention.
» Sleep-related conditions, e.g., parasomnias; narcolepsy.
» Migraine associated disorders, e.g., migraine with visual aura.

See https://www.epilepsydiagnosis.org/epilepsy-imitators.html for a full list of conditions which may look like an epileptic seizure.

LoE:IVb[xxii]

Not all persons who have an epileptic seizure have epilepsy. Specific criteria must be met to diagnose epilepsy (see Section14.6: Epilepsy).

DIAGNOSIS

Epileptic seizures are diagnosed clinically, through eye-witness accounts, videos, careful observation by the healthcare professional, and a history from the patient of the symptoms, signs and behaviours experienced prior to and during the seizure. Epileptic seizures are classified by the International League Against Epilepsy (ILAE) into three types: focal, generalised, and unknown (first level in Figure 1). The evolution of the seizure (how it starts and progresses clinically) directs special investigations to determine the cause of the seizure and related management.

LoE:IVb[xxiii]

SEIZURE TYPES

Focal seizures:

The epileptic activity arises from a particular focus, or networks limited to one hemisphere of the brain.

Focal seizures may present with motor signs (e.g., rhythmic jerking of one limb; automatisms such as lip-smacking) or with non-motor signs (e.g., olfactory, tactile, or visual hallucinations, or intense emotions such as fear). This depends on the site of origin, which may be the frontal lobe, temporal lobe, parietal lobe or occipital lobe. A focal brain lesion should always be excluded in new focal seizures.

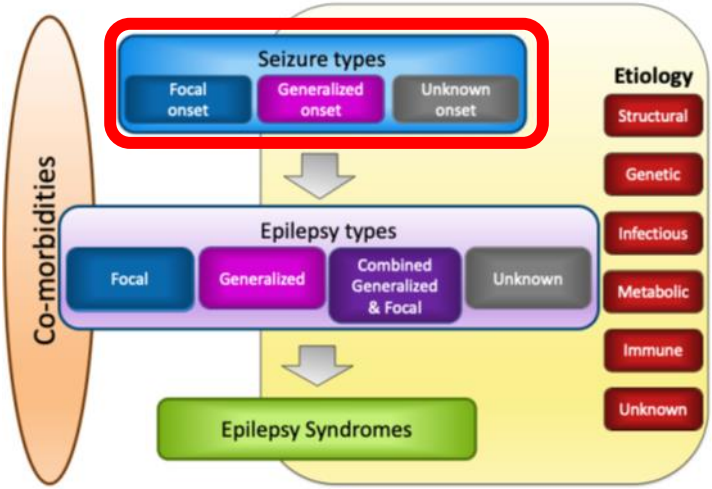


Figure 1. International League Against Epilepsy classification of seizure types *(Source: Scheffer IE, Berkovic S, Capovilla G, Connolly MB, French J, Guilhoto L. ILAE classification of epilepsies: Position paper of the ILAE Commission for Classification and Terminology. Epilepsia. 2017, 58 (4): 512-521)*

LoE:IVb[xxiv]

Focal seizures are classified according to the degree of impaired consciousness and whether there is progression to a tonic-clonic seizure. Consciousness is evaluated by assessing the levels of awareness (of themselves and their surroundings) and responsiveness (to other people or stimuli) of the person during the seizure. Any impairment in consciousness means that the person's safety and the safety of others must be protected during the seizure.

- **Focal preserved consciousness seizures** (previously termed 'simple partial seizures'): the person is fully aware of themselves and their surroundings and fully responsive to others throughout the seizure.
- **Focal impaired consciousness seizures:** (previously termed 'complex partial seizures'), the person has impaired awareness or responsiveness at any time during the seizure.
- **Focal unknown state of consciousness seizures:** used when the state of consciousness is not known (e.g. unclear information).
- **Focal-to-bilateral tonic-clonic seizure:** the epileptic seizure progresses to both brain hemispheres. Bilateral tonic-clonic seizures are differentiated from generalised tonic-clonic seizures by a history of preceding focal signs (either sensory or motor) occurring before complete loss of consciousness and the development of tonic-clonic movements. The terms 'aura' or 'warning signs' may be used by people for the focal signs of the seizure.

Generalised seizures
The epileptic activity arises within and rapidly spreads to involve networks in both hemispheres of the brain. Generalised seizures are almost always associated with impaired or loss of consciousness.
Generalised seizures are classified as:

» **Generalised motor seizures**, which include:
  – **Generalised tonic-clonic seizures**, with loss of consciousness and bilateral tonic-clonic limb movements.
  – **Generalised seizures other than tonic-clonic**, including seizures with varying degrees of impaired consciousness and bilateral *tonic* movements (stiffening, sometimes with vibratory movements) of limbs or eyes, bilateral *atonic* movements (sudden loss of muscle tone) of head, trunk or limbs, bilateral jerks (brief shock-like muscle contractions), as in *myoclonic* seizures
» **Absence seizures** (previously termed 'petit-mal seizures'), which usually occur in association with an epilepsy syndrome (See Section14.6: Epilepsy). Absence seizures may be:
  – **'typical'** with abrupt loss of consciousness lasting 5-30 seconds and clonic movements of face and/or automatisms, or
  – **'atypical'** with a less abrupt onset of impaired consciousness, longer seizure duration and loss of muscle tone of head, trunk and limbs. Atypical absence seizures are rare and can be challenging to differentiate from focal sensory seizures.

LoE:IVb[xxv]

Unknown:
The category of 'unknown onset' is used when there is not enough information, or the clinical presentation is too unclear, to distinguish between focal or generalised seizures.

For more detail and educational videos on seizure types, see https://www.epilepsydiagnosis.org/seizure/seizure-classification-groupoverview.html

14.5 STATUS EPILEPTICUS
G41.0-2; G41.8-9

DESCRIPTION
In status epilepticus, the seizures do not stop, or they occur repeatedly in close succession with impaired consciousness between seizures. Status epilepticus may be 'convulsive' (associated with prominent motor symptoms) or 'non-convulsive' (i.e., without prominent motor symptoms).

Convulsive status epilepticus:
Convulsive status epilepticus is defined as ≥ 5 minutes of either:
» a continuous generalised, or bilateral tonic clonic seizure, or
» two or more discrete generalised, or bilateral tonic clonic seizures with incomplete recovery of consciousness between the seizures.

Convulsive status epilepticus is a **medical emergency**. There are two critical time points:
» Time point 1: **5 minutes** from the onset of the initial epileptic seizure (i.e., at the point of diagnosis). Immediate treatment is needed to prevent ongoing epileptic seizure activity.
» Time point 2: **30 minutes** of epileptic seizure activity, timed from the onset of the seizure. After 30 minutes of seizure activity, irreversible brain damage related to hypoxia, acidosis, depletion of local energy stores, cerebral oedema and structural damage, is likely to occur.

Complications of convulsive status epilepticus include:
» hyperpyrexia
» respiratory depression
» cerebral oedema
» blood pressure disturbances
» inappropriate antidiuretic hormone (ADH) secretion
» hypoxic ischaemic damage to brain, myocardium and muscles.
» disturbances of blood glucose
» renal failure
» acidosis

Non-convulsive status epilepticus:
Non-convulsive status epilepticus refers to abnormally prolonged or rapidly recurring epileptic seizures with impaired consciousness but no major motor symptoms (e.g., focal seizures with autonomic, sensory or perceptual manifestations or absence seizures). The presentation is often subtle, and the seizures may not be recognized. Diagnosis is confirmed on EEG. Treat as for convulsive status epilepticus below. See Section14.5.1: Epileptic seizures and status epilepticus in adolescents (13 – 18 years) and adults. Identify and manage all underlying causes.

Causes of epileptic seizures and status epilepticus

With every epileptic seizure, the underlying cause of the seizure must be determined and treated, including in people with epilepsy.

Important causes of epileptic seizures that must be considered include:
» Infectious conditions e.g., meningitis or encephalitis.
» Encephalopathy e.g., hypertensive encephalopathy or cerebral hypoxia
» Metabolic conditions e.g., hypoglycaemia, hypo- or hypernatraemia, hypocalcaemia.
» Brain lesions e.g., brain tumours, stroke and post-stroke sequelae, trauma and post-traumatic sequelae
» Substance withdrawal e.g., alcohol or benzodiazepines.

» Substance intoxication e.g., cocaine or amphetamines.
» Poisoning or toxin ingestion (accidental or intentional as in an overdose) e.g. isoniazid.
» Other neurological (e.g., cerebral palsy) or neurodegenerative (e.g., Alzheimer's dementia) conditions.
» Suboptimal treatment of epilepsies e.g., breakthrough seizures, treatment non-adherence, recent changes to antiseizure medicine (ASM), antiseizure medication toxicity.

14.5.1 EPILEPTIC SEIZURES AND STATUS EPILEPTICUS IN ADOLESCENTS (13 – 18 YEARS) AND ADULTS

Additional causes of epileptic seizures to consider in adolescents and adults are categorised below:

Pregnancy related	Infections	Substances & poisoning
» eclampsia (See Section6.4.2: Eclampsia) » electrolyte abnormalities (e.g., in hyperemesis gravidarum) » stroke » reduced blood concentrations of antiseizure medication	» meningitis » encephalitis » brain abscess » neurocysticercosis	» substance abuse (e.g. cocaine, amphetamines) » withdrawal syndromes (e.g., benzodiazepine, alcohol) » medicine toxicity and overdose (e.g., antiseizure medications, antidepressants, antipsychotics, isoniazid) » environmental toxins (e.g. pesticides)
Metabolic conditions	**Systemic disorders**	**Primary cerebral causes**
» hypoglycaemia » hypocalcaemia » hypomagnesaemia » hyponatraemia » hypernatraemia	» vasculitis » hypertensive encephalopathy » uraemia (renal failure) » hyperammonaemia (liver failure)	» tumour » trauma » neurodegenerative conditions » idiopathic/unknown

Special considerations

Adolescents and young adults:

» High risk for substance intoxication or withdrawal, and traumatic brain injuries.
» Mental health conditions are common, and may present as 'epilepsy imitators' (see differentials of epileptic seizures above and https://www.epilepsydiagnosis.org/epilepsy-imitators.html).
» Idiopathic generalised epilepsies (including epilepsy with generalised tonic-clonic seizures, juvenile myoclonic epilepsy, juvenile absence epilepsy) may first present in this age group.
» High risk for poor adherence to ASMs and breakthrough seizures.

» Often require intensive individual and family counselling and support, with appropriate involvement of social welfare and education sectors.

Girls and women in child-bearing age group:

» Exclude pregnancy and pregnancy related complications.

» ASM concentrations may become sub therapeutic in pregnant women with epilepsy, causing breakthrough seizures. An increase in ASM dose may be required during pregnancy (reduce dose after delivery). Where possible monitor.

CAUTION

Children born to women taking valproate are at significant risk of birth defects (11%) and persistent developmental disorders (40%). Valproate is contra-indicated and should be avoided in pregnancy and in adolescents and women of child-bearing potential.

LoE:IIIb[xxvi]

People > 65 years of age

» Common reversible conditions include metabolic abnormalities, medications, alcohol withdrawal.

» The risk of developing epilepsy increases with age. Epilepsy in this age group is commonly caused by stroke, brain tumours and dementias. Continued ASM may be advisable after a single seizure in these patients.

GENERAL MEASURES

On arrival/ while fitting:

» Ensure the environment is safe. Remove all sharp objects and hot liquids.

» Place the patient in a lateral position to prevent aspiration of secretions or vomitus, on the floor if necessary (see figure 2).

» Do not place anything (spoon or spatula, etc.) in the patient's mouth.

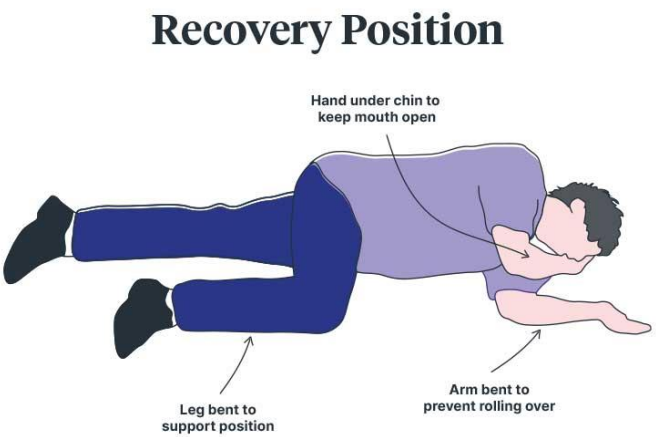


Figure 2: Recovery position for adults experiencing a seizure
Source: Ausmed: Adult Basic Life Support

LoE:IVb[xxvii]

» Obtain an eyewitness account of the seizure onset and any associated impaired consciousness. **If seizure duration is ≥ 5 minutes, commence urgent medicine treatment for convulsive status epilepticus** (refer to Table 1 on medicine management and supportive care of status epilepticus in adolescents and adults).
» Ensure the airway is not obstructed and administer oxygen via face mask or nasal cannula to maintain SaO_2 ≥ 95%.
» Intubation should be performed if airway, ventilation, or oxygenation cannot be maintained, or if seizure is prolonged.
» Examine for fever, dehydration, meningism, hypoglycaemia, evidence of toxin or poison ingestion, head, neck or other trauma, obvious focal neurology and other possible causes of the seizure.
» Secure intravenous access.
» Monitor vital signs every 15 minutes.
» Keep nil per mouth.
» Ensure the family/caregiver/escort is attended to; social worker or auxiliary staff member should obtain all contact details and provide counselling as needed.

Convulsive status epilepticus:
If the seizure does not resolve by 5 minutes of its onset, commence urgent medicine treatment.

MEDICINE TREATMENT

Aim to control the seizure within 30 minutes of its onset, prevent complications of status epilepticus with supportive care, and identify and correct underlying causes. Follow standard resuscitation protocols, such as the ABCDE approach.

TABLE 1: MEDICINE MANAGEMENT AND SUPPORTIVE CARE OF STATUS EPILEPTICUS IN ADOLESCENTS AND ADULTS

PHASE	MANAGEMENT	SUPPORTIVE CARE
EARLY STATUS EPILEPTICUS (5 – 10 minutes)	**LEVEL 1 INTERVENTION:** (Benzodiazepines) If IV access: • Lorazepam, IV, 4 mg, administered not faster than 2 mg/minute. *LoE:IIb[xxviii]* **OR** • Midazolam, IV, 10 mg. *LoE:IIb[xxix]* **OR** • Diazepam, IV, 10 mg administered over at least 5 minutes (not faster than 2mg/min). **OR** *LoE:IIb[xxx]* • Clonazepam, IV, 1 mg. *LoE:IIIb[xxxi]* If no IV access: • Midazolam, 10 mg, IM or buccal, using the parenteral formulation, while continuing to establish IV access If no IV access and no midazolam is available: • Clonazepam, IM, 1 mg. *LoE:IVb[xxxii]* **OR** • Diazepam, rectal, 0.2 – 0.5 mg/kg as a single dose (maximum 20 mg/dose). *LoE:IVb[xxxiii]* If the seizure does not resolve 5 minutes after first dose of benzodiazepine, repeat the dose of benzodiazepine. If seizure aborts after 1 or 2 doses of benzodiazepines, but patient is at high risk of recurrent seizures (e.g., known with epilepsy and defaulted treatment), load with antiseizure medicine.	» Stabilize and support airway breathing and circulation. » Identify and treat the underlying cause of seizures such as: – Hypoglycaemia. – Electrolyte derangements (e.g. calcium, sodium, potassium, magnesium and urea). – Poisoning. – Intoxication/overdose (e.g. isoniazid, theophylline, tricyclic antidepressants, cocaine, methamphetamine). – Withdrawal syndromes (e.g. alcohol, benzodiazepines). » If patient is known with epilepsy and on treatment take blood for measurement of ASM levels.

	CAUTION Benzodiazepines can cause respiratory depression. Monitor closely for respiratory depression. If this occurs, assist ventilation with bag-valve mask (1 breath every 3–5 seconds) and refer urgently/transfer to a high-care setting.	
ESTABLISHED STATUS EPILEPTICUS (10 – 30 minutes)	**LEVEL 2 INTERVENTION:** (Antiseizure medicine.) If IV access **and not suspected to be drug- or toxin-induced**: • Phenytoin, IV, 20 mg/kg diluted in 200 ml sodium chloride 0.9% **(not dextrose containing fluid)** administered not faster than 50mg/minute (usually 20–30 minutes) with cardiac monitoring. ○ If arrhythmias/hypotension occur, interrupt infusion temporarily and reintroduce at a slower rate. **CAUTION** Do not use phenytoin to manage suspected drug- or toxin-induced seizures. Cardiac monitoring is mandatory to ensure safe use. *LoE:IVb*[xxxiv] **Note:** » **Do not use phenytoin if seizures are suspected to be drug- or toxin-induced.** To manage, proceed to level 3 intervention, refractory status epilepticus, and address the acute poisoning (see Chapter 19: Poisoning). » If phenytoin toxicity is suspected (e.g. in a patient on chronic phenytoin treatment), proceed to level 3 intervention, refractory status epilepticus. If no IV access, consider: » Levetiracetam oral, crushed and given by nasogastric tube, 60 mg/kg as a single dose. (Maximum dose: 4500 mg.)	» Prepare for intubation/ventilation. » Arrange referral to higher level of care.

	LoE:IVb[xxxv]	
REFRACTORY STATUS (30 – 60 minutes)	• Propofol, IV, 1–2 mg/kg/dose as a bolus, followed by a continuous infusion at 1.2 mg/kg/hour. If necessary, titrate to effect by increasing infusion rate by 0.3 to 0.6 mg/kg/hour every 5 minutes (maximum rate of 12 mg/kg/hour or maximum total dose of 4 mg/kg/hour over 48 hours). LoE:IVb[xxxvi] **OR** • Midazolam, IV, 0.1 – 0.2 mg/kg bolus, followed by 0.05 – 0.5 mg/kg/hour infusion, titrated to effect. LoE:IVb[xxxvii] **Note:** » To prevent recurrent seizures if epilepsy is diagnosed or suspected, continue treatment with the most appropriate antiseizure medication during the infusion and weaning of propofol or midazolam. » Continue propofol or midazolam infusion for 12−24 hours after the last clinical or electrographic seizure, then wean the infusion.	» Admit to high- or intensive-care unit, if possible. » Employ a neuroprotective ventilation strategy (See Chapter 23: Adult Critical Care): – If it is necessary to ventilate, maintain PaCO2 in the low-normal range, i.e. 4.0–4.5 kPa. » Monitor: – heart rate, acid-base status, – respiratory rate, blood gas analysis, – blood pressure, SaO2, – electrolytes, neurological status, – blood glucose, fluid balance, – antiseizure medication blood concentrations, osmolality.

After The Seizure

Post Ictal Phase:

» Keep nil per mouth and haemodynamically stable until patient has regained consciousness and is aware of themself and their surroundings.
» If there is agitation or disturbed behaviour, consider post-ictal delirium and manage as for delirium – see Section20.8: Delirium.
» Clarify the cause of the seizure and manage appropriately. Further investigations (e.g., lumber puncture and neuroimaging) are driven by clinical signs and seizure onset (e.g., focal onset).
  » If meningitis is suspected, commence antibiotic therapy urgently.
  » Counsel the patient and their family regarding the cause of the seizure, management given and likely sequelae of the seizure. Offer only as much information as the family or patient is able to receive at that time.
  » If reversible causes of the epileptic seizure have been addressed, wean and stop ASMs. Consider whether the person meets the criteria for a diagnosis of epilepsy (see Section14.6: Epilepsy) and requires ongoing ASMs.
» On discharge, set up a follow-up appointment to reinforce the counselling messages.

Active follow up:

» Wean any residual ASMs, unless ongoing maintenance treatment is indicated, or epilepsy has been diagnosed.

REFERRAL

» Refractory status.
» Need for more intensive care than can be provided at the facility.

14.6 EPILEPSY

G40.0-9

DESCRIPTION

Epilepsy is a disease of the brain defined by any of the following conditions:

» At least two unprovoked (or reflex) seizures occurring >24 hours apart, or
» One unprovoked (or reflex) seizure if there is a high risk (60% or more) of having recurrent seizures within the next 10 years (i.e., if the person is vulnerable to having another unprovoked seizure, e.g. because of structural damage such as from a stroke) or
» Diagnosis of an epilepsy syndrome.

Note:

» An "unprovoked" epileptic seizure is a seizure which does not have evidence of an identifiable temporary or reversible factor acting on a healthy brain (e.g., hypoglycaemia, alcohol withdrawal, concussion).

» A "reflex" epileptic seizure is a seizure which occurs in response to a stimulus such as flashing lights. Such epileptic seizures indicate the person's brain is predisposed to having seizures and therefore warrant a diagnosis of epilepsy.

» Epilepsy may be diagnosed after a single unprovoked seizure in people with an increased risk of recurrence for example in people with previous [MR1] [JR2] [MR3] conditions such as TB meningitis, neurocysticercosis, stroke, brain tumour or traumatic brain injury. Note that the single unprovoked seizure is not caused by the immediate insult to the brain but occurs spontaneously (i.e., is unprovoked) because of the long-term sequelae of the initial insult. The damaged brain is thus at high risk of a recurrent unprovoked epileptic seizure.

» Epileptic syndromes confer a diagnosis of epilepsy, even if the risk of recurrent epileptic seizures is low for a particular individual.

» Epilepsy is considered to be resolved and no longer needing maintenance treatment in individuals who either:
  – had an age-dependent epilepsy syndrome, but are now past the applicable age, **OR**
  – have remained seizure-free for the last 10 years and weaned off ASM for at least the last 5 years.

» Epilepsy is associated with many psychological, social and legal problems, and cultural misperceptions which should be explored and addressed at the time of diagnosis and throughout the course of the illness.

Epilepsy types

As shown in Figure 3, epilepsies are classified by the International League Against Epilepsy (ILAE) according to:

» Type of seizures experienced, e.g., focal, generalised, combined generalised and focal, or unknown.

AND

» Aetiology, which may be:
  – Structural (e.g., cerebral or vascular malformations, stroke, traumatic brain injury, brain tumours).
  – Genetic (the epilepsy is a direct result of chromosomal or gene abnormalities, e.g., Down syndrome, Fragile X syndrome, Dravet syndrome).
  – Infectious (e.g., post-infectious sequelae of TB meningitis).
  – Metabolic (e.g., inborn errors of metabolism).
  – Immune (rare conditions involving neuroreceptor antibodies).
  – Unknown.

Focal epilepsy

Characterised by unprovoked focal seizures, which may or may not evolve to bilateral tonic-clonic seizures. The diagnosis is made clinically and requires a detailed description of how the seizure started. In people presenting with generalised tonic-clonic seizures, it is important to ask about any warning symptoms or 'aura' experienced by the person before losing consciousness. Typical interictal and/or ictal EEG findings may be present, and neuroimaging may reveal a focal brain lesion, supporting the diagnosis, but may also be normal.

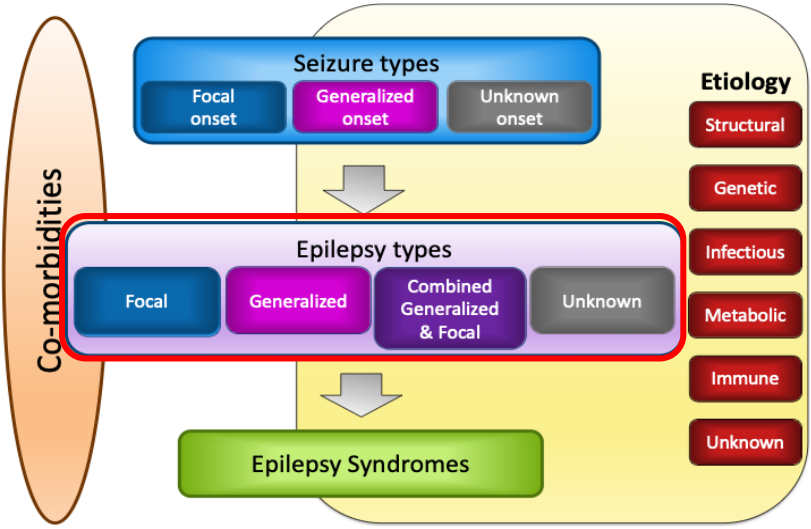


Figure 3. International League Against Epilepsy classification of seizure types *(Source: Scheffer IE, Berkovic S, Capovilla G, Connolly MB, French J, Guilhoto L. ILAE classification of epilepsies: Position paper of the ILAE Commission for Classification and Terminology. Epilepsia. 2017, 58 (4): 512-521)*

LoE:IVb[xxxviii]

Generalised epilepsy

Characterised by unprovoked generalized seizures, including tonic-clonic, tonic, myoclonic, and absence seizures. Typical interictal and/or ictal EEG findings may be present.

Combined generalised and focal epilepsy

Diagnosed in people with more than one type of seizure, e.g. unprovoked focal seizures and unprovoked generalised seizures. This may occur in people with Dravet syndrome or Lennox-Gastaut syndrome.

Unknown epilepsy
This classification is used when it is not possible to determine whether the epilepsy is focal, generalised, or combined generalised and focal epilepsy from the available history, clinical, and investigative findings.

For seizure types, see Section14.4: Epileptic seizures.
For more information and educational videos on epilepsy types, see https://www.epilepsydiagnosis.org/epilepsy/epilepsy-classification-groupoverview.html

Investigations:

» Neuroimaging (a CT Brain or MRI if available) should be conducted:
  – in new focal onset seizures to exclude a focal brain lesion.
  – if the epilepsy features change in an individual (i.e., new symptoms appear, noting that most people will experience the same march of symptoms with each seizure).
  – if epileptic seizures recur despite adherence to treatment and the diagnosis is unclear.
» EEG is indicated for recurrent or syndromic seizures where a diagnosis cannot be made on clinical grounds alone. Delay an EEG for at least one week after the convulsive episode.
» EEG is not indicated for simple febrile seizures.
» If the seizure presentation is atypical, a 12-lead ECG should be considered to identify prolonged QT interval syndromes. Syncope with exercise, syncope in response to loud noise, fright, or extreme emotional stress, syncope whilst supine, a family history of sudden death in a young person e.g. <40 years old, or sensorineural deafness are associated with some types of long QT syndrome.

14.6.1 EPILEPSY IN ADOLESCENTS AND ADULTS

G40.0-9

DESCRIPTION

See Section14.6: Epilepsy.

DIAGNOSTIC CRITERIA

» The diagnosis of epilepsy is usually made clinically.
» Take an adequate history and get an accurate witness description of the seizures to define the type of epilepsy.
» Juvenile myoclonic epilepsy and absence seizures specifically should be considered and identified, as some first line medicines may be less efficacious or may even worsen seizure frequency or severity.
» Patients with new onset epilepsy should have a CT scan (essential in immunocompromised patients), and other investigations as clinically indicated.

Special considerations

Women and girls of child-bearing potential and pregnancy

» Antiseizure medicines during pregnancy can cause structural or physical malformations and neurodevelopmental harms that may impact learning and education.
» The risk of antiseizure medicine to the unborn child needs to be balanced against the risk of uncontrolled seizures to both the mother and unborn child.
» The risk associated with each antiseizure medicine during pregnancy differs (see Figure 4).

It is crucial to treat epilepsy during pregnancy to prevent seizures, which pose significant risks to both the mother and the fetus/infant.

» Women and girls of child-bearing potential with epilepsy should be counselled regarding contraception and the need to plan pregnancy.
  – NOTE: There are important drug-drug interactions between hormonal contraceptives (except DMPA) and several anticonvulsant medicines (e.g. carbamazepine, phenobarbital, phenytoin).
  – Progestin-only injectable contraceptives or IUCDs are the preferred contraceptive methods for women of child-bearing potential on ASMs. See Chapter 7: Family planning.
» In pregnant women, women of child-bearing potential (i.e. women < 55 years of age), and young girls who are likely to need to continue treatment into their child-bearing years, initiate treatment with a lower risk ASM.
  – Lamotrigine and levetiracetam are the safer ASM to use.
  – Large amounts of data consistently show no increased risk of major congenital malformations associated with the use of lamotrigine or levetiracetam at usual doses.
  – Since lamotrigine requires slow dose titration, initiation of lamotrigine is best suited to low-risk patients who have infrequent seizures, and no previous history of seizures requiring hospitalisation or status epilepticus.
  – Levetiracetam may be used if there is a poor response or adverse effects to lamotrigine, or in high-risk patients with frequent seizures, a previous history of hospitalization for seizures or status epilepticus.
» Valproate **must not** be used in pregnant women, women of child-bearing potential and young girls who are likely to need to continue treatment into their child-bearing years.
  – In women who take valproate while pregnant, around 1 in 9 babies (11%) will have a major birth defect and about 3–4 children in every 10 may have neurodevelopmental problems and these disorders can be seriously debilitating and permanent (e.g., delayed leaning

to walk and talk, lower intelligence, poor speech and language skills, memory problems, autism or autism spectrum disorders, attention deficit hyperactivity disorder).

- In situations where valproate is deemed the only option in a female patient after all other treatment options have been ruled out, health professionals (prescribers and dispensers) are required to:
  - Regularly review treatment
  - Provide counselling on the risks of valproate use in pregnancy
  - Ensure that the woman has completed and signed an acknowledgment of risk form annually: https://www.sahpra.org.za/wp-content/uploads/2025/05/GLF-CEM-PV-S01_v2-Valproate-Annual-Risk-Acknowledgement-Form-ARF.pdf
  - Provide supplemental folic acid, oral, 5 mg daily.

» Women and girls with epilepsy who discover they are pregnant should not abruptly stop their ASM due to the risk of seizures.

- Women and girls who become pregnant while on valproate should be transitioned off valproate and onto levetiracetam, as early as possible during pregnancy, to decrease the risk of neurodevelopmental harms, provided their seizures are not refractory to other ASM.

» During pregnancy women may experience an increased number of seizures.

- This may be due to sleep deprivation, increased emotional stress and changes in ASM plasma concentrations.
- ASM plasma concentrations may decrease during pregnancy due to decreased absorption from nausea and vomiting, increased volume of distribution and increased clearance.
- There is increased hepatic metabolism of lamotrigine and increased renal clearance of levetiracetam in pregnancy, which return to normal post-partum; increase the dose if necessary, according to clinical response.

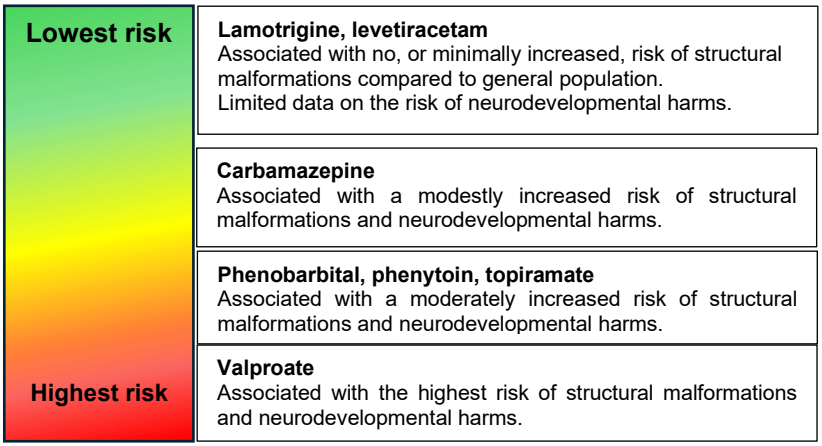


Figure 4. Risk of congenital structural malformations and neurodevelopment harms associated with various antiseizures medicines.
Increasing risk refers to increasing number of pregnancies or children affected.
(Adapted from Pennell PB. *Neurotherapeutics*. 2016 and Medicines & Healthcare products Regulatory Agency safety leaflet).

LoE:IVb[xxxix]

CAUTION – ASM and pregnancy

Children born to women taking valproate are at significant risk of birth defects (11%) and persistent developmental disorders (40%).
Valproate is contra-indicated and should be avoided in pregnancy and women of child-bearing potential.

LoE:IIIb[xl]

Children and adolescents transitioning to adult care

» Children and adolescents whose seizures are controlled on levetiracetam should be continued on levetiracetam in adulthood.

Adults on ART

» Lamotrigine is the preferred ASM in people with HIV on ART because of fewer medicine interactions.
» Phenytoin, phenobarbital and carbamazepine are enzyme inducing ASMs. Due to potential drug interactions with ARVs, switch these medicines to lamotrigine.
» Where concurrent use of dolutegravir and carbamazepine, phenytoin, or phenobarbital is unavoidable, double dolutegravir dose to 50 mg 12-hourly.

» Metabolism of lamotrigine is induced by lopinavir/ritonavir and atazanavir/ritonavir. The dose of lamotrigine may need to be increased when patients are switched to, or initiated on, lopinavir/ritonavir or atazanavir/ritonavir.

GENERAL AND SUPPORTIVE MEASURES

» Patients should record dates and, if possible, times of seizures in a seizure diary. Review seizure diary at each consultation for assessment of therapy.
» Patients with epilepsy should be issued a disease identification bracelet, necklace or card.
» Patients with uncontrolled seizures should avoid driving, swimming, working at heights and operating machinery until they have been seizure free for at least one year. Refer to an occupational therapist for rehabilitation and a workplace assessment. The patient should sign in the medical notes that they have received workplace and lifestyle advice.
» Provide counselling and advice on:
  – the adverse effect of alcohol on seizures,
  – sleep hygiene,
  – the effect of missing a dose of medication,
  – discontinuing the medication without advice of a doctor.

MEDICINE TREATMENT

Acute treatment

Manage acute seizure and status epilepticus as per seizures/status epilepticus (see Sections 14.4: Epileptic seizures, and 14.5: Status epilepticus).

Maintenance Treatment

» Refer to Table 2 below for guidance around the choice of medicine by seizure type.
» HIV status, child-bearing potential and pregnancy are important determinants of medicine choice.
» The antiseizure treatment strategy should also be individualised based on use of other medicines, comorbidities, as well as response to medication, and adverse effects.
» The goal of medicine treatment is to prevent recurrent seizures and optimise quality of life.
» As a general rule, a single ASM (monotherapy) is best. Progressively increase the dose of the ASM until the seizures are controlled or clinically important side effects occur.
» Recommended drug doses are general guides and will be effective in most patients. However, some patients may need much higher or lower doses. Doses should be increased at 2-weekly intervals only.

» If the initial ASM fails to achieve satisfactory control (no seizures) at optimal dosages, or causes unacceptable adverse effects, then a trial of a second ASM medicine may be commenced.
» Initiate second medicine, titrate to therapeutic dose; then gradually reduce and stop the first ASM over 6–8 weeks or longer if necessary (See notes below for individual medicines).
» Failure of second-line monotherapy, after exclusion of alcohol use/misuse and poor adherence, may require add-on therapy. Add on therapy may be initiated by a medical officer in consultation with a specialist.

Medicine interactions

Phenytoin, phenobarbital and carbamazepine are potent enzyme inducing agents and should be used with caution with other medicines metabolised by the liver, especially warfarin, antiretrovirals, progestin subdermal implants and oral contraceptives.

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» Therapeutic drug monitoring is not necessary in stable patients, but should be performed in the following situations:
  – To confirm ASM toxicity in a symptomatic patient.
  – In patients with poor seizure control.
  – To confirm suspected poor adherence despite self-reported good adherence.
» Phenytoin is not recommended in Table 2, however may be continued in adults whose seizures are well-controlled on phenytoin. Therapeutic drug monitoring should be conducted in patients receiving higher than usual doses of phenytoin.
» Long term use of phenytoin and carbamazepine are associated with potential risks. Continued use of these ASM requires careful consideration of the balance between benefits and risks in individual patients.

Table 2: Epilepsy treatment in adolescents and adults

Epilepsy type		Population	1st line	2nd line	3rd line *(specialist consultation)*	Comments
Focal epilepsy	With and without evolution to bilateral tonic-clonic seizures	Adolescent boys, men and women not able to have children	Lamotrigine	Carbamazepine **OR** Levetiracetam	Consider combination treatment or add-on topiramate.	Avoid carbamazepine in people with HIV on ART due to drug-drug interactions.
		Pregnant women and women of child-bearing potential	Lamotrigine	Levetiracetam	Consider Carbamazepine **OR** Combination of lamotrigine and levetiracetam **OR** add-on topiramate	Avoid carbamazepine in people with HIV on ART due to drug-drug interactions.
Generalised epilepsy	Tonic-clonic, atonic, clonic or tonic seizures	Adolescent boys, men and women not able to have children.	Lamotrigine (low-risk) **OR** Levetiracetam (high-risk)	Lamotrigine or levetiracetam (whichever not used as first line) **OR** Valproate	Discuss with specialist Consider: Combination therapy **OR** Add-on topiramate	Valproate should not be used unless lamotrigine and levetiracetam are poorly tolerated or ineffective. If valproate used in girls 10 years and older - see note below on acknowledgement of risk form.
		Pregnant women and women of child-bearing potential	Lamotrigine (low risk) **OR** Levetiracetam (high-risk)	Levetiracetam or lamotrigine (whichever not used as first line) **OR** Consider combination therapy with lamotrigine and levetiracetam	Refer for specialist assessment and intervention	Valproate should not be used unless lamotrigine or levetiracetam alone or in combination are ineffective or poorly tolerated.
	Myoclonic *Confirm diagnosis and discuss management*	Adolescent boys, men and women not able to have children	Valproate	Lamotrigine	Discuss with specialist Consider levetiracetam **OR**	These seizures may be aggravated by phenytoin or carbamazepine. Lamotrigine may be effective but may also exacerbate myoclonic seizures.

	with a specialist				Consider combination therapy.	If valproate used in girls 10 years and older - see note below on acknowledgement of risk form.
		Pregnant women and women of child-bearing potential	Lamotrigine	Levetiracetam	Discuss with specialist Consider combination therapy	These seizures may be aggravated by phenytoin or carbamazepine. Lamotrigine may be effective but may also exacerbate myoclonic seizures.
	Absence *e.g. Juvenile absence epilepsy or persistent childhood absence epilepsy*	Adolescent boys, men and women not able to have children	Valproate	Lamotrigine	Discuss with specialist Consider levetiracetam **OR** Consider combination therapy.	These seizures may be aggravated by phenytoin or carbamazepine If valproate used in girls 10 years and older - see note below on acknowledgement of risk form.
		Pregnant women and women of child-bearing potential	Lamotrigine	Levetiracetam	Discuss with specialist Consider combination therapy **OR** Consider valproate	Valproate should not be used unless lamotrigine or levetiracetam alone or in combination are ineffective or poorly tolerated. If valproate is used, see note below on "Acknowledgement of risk form" and effective family planning. These seizures may be aggravated by phenytoin or carbamazepine
Combined generalised and focal epilepsy OR Unknown/unclassified Discuss clinical presentation and management with a specialist in all cases.						

NOTE:

- Lamotrigine is the preferred first line treatment for all adult patients, including women of child-bearing potential, pregnant women, and people living with HIV.
- Lamotrigine requires slow dose up-titration and may not be suitable in people at high-risk of seizures. High-risk patients are those with frequent seizures, a previous history of hospitalization for seizures, or previous history of status epilepticus. Low-risk patients are those with infrequent seizures, no previous hospitalization for seizures, and no history of status epilepticus.
- **If valproate is used, acknowledgment of risk must be obtained annually, even if not of child-bearing potential. Girls aged 10 years and older should receive effective family planning and consider a long-acting form of contraception.** https://www.sahpra.org.za/wp-content/uploads/2025/05/GLF-CEM-PV-S01_v2-Valproate-Annual-Risk-Acknowledgement-Form-ARF.pdf

*Assess level of risk (high vs low) based on clinical judgement and discuss with a specialist if unsure. In general, high-risk patients are those with frequent seizures, a previous history of hospitalization for seizures, or previous history of status epilepticus. Low-risk patients are those with infrequent seizures, no previous hospitalization for seizures, and no history of status epilepticus.

LoE:IVb[xiii]

Medicine Treatment

- Lamotrigine, oral (Doctor initiated).
  - Dose-titrate using table below.

Table 3: Dosing table for lamotrigine as monotherapy or add-on therapy:

	Week 1 and 2	Week 3 and 4	Maintenance dose
Monotherapy	25 mg daily	50 mg daily	100–200 mg (once a day or two divided doses). To achieve maintenance, doses may be increased by 50–100 mg every 1–2 weeks.
Lamotrigine as add on therapy to existing regimen			
Add on therapy where **regimen does not include** valproate or other inducers/inhibitors of lamotrigine glucuronidation	25 mg daily	50 mg daily	100–200 mg (once a day or two divided doses). To achieve maintenance, doses may be increased by 50–100 mg every 1–2 weeks.
Add-on therapy where **regimen includes ASMs that induce glucuronidation** *(e.g. phenytoin, carbamazepine, phenobarbital, etc.)*	50 mg daily	100 mg in two divided doses	200–400 mg (two divided doses). To achieve maintenance, doses may be increased by 100 mg every 1–2 weeks.
Add-on therapy where **regimen contains valproate** *(regardless of other concomitant medication)*	25 mg on alternate days.	25 mg daily	100–200 mg (once a day or two divided doses). To achieve maintenance, doses may be increased by 25–50 mg every 1–2 weeks.

Note:

» If therapy is interrupted for more than a week, restart the titration protocol.

» Metabolism of lamotrigine is induced by lopinavir/ritonavir and atazanavir/ritonavir. The dose of lamotrigine may need to be increased when people with HIV are switched to or initiate lopinavir/ritonavir or atazanavir/ritonavir.

» Metabolism of lamotrigine is induced during pregnancy. The dose of lamotrigine may need to be increased during pregnancy.

LoE:IVb[xliii]

CAUTION - LAMOTRIGINE

Lamotrigine may cause Stevens-Johnson Syndrome.

LoE:IVb[xliv]

- Carbamazepine, oral

o Start with 100 mg 12 hourly.
o Increase by 100–200 mg/day at weekly intervals according to seizure control and adverse events.
o Usual maximal dose: 600 mg 12 hourly. *LoE:IIIb*[xiv]

- Levetiracetam, oral

o Initially 250 mg 12 hourly, increasing to a therapeutic dose of 500 mg 12 hourly.
o Dose can be adjusted upwards in increments of 500 mg 12 hourly every 2 to 4 weeks to a maximum of 1500 mg 12 hourly (3000 mg per day).

- Valproate, oral

o Usual starting dose: 200–300 mg 12 hourly.
o Increase, as required, every 3 days to 2 weeks (depending on the seizure frequency) to a maximum dose of 1200 mg 12 hourly.

- Phenytoin, oral, 4.5–5 mg/kg (lean body mass) daily, at night.

Only consider continuing phenytoin in patients already well controlled on phenytoin, and in whom phenytoin is well tolerated.

o Usual starting and maintenance dose in adults: 300 mg once daily.
o Dose increases above 300 mg should be done in no more than 50 mg increments at intervals no shorter than 2 weeks.
o Doses > 300 mg/day of phenytoin are potentially toxic and could lead to permanent cerebellar damage. Caution and frequent monitoring of drug levels are essential at doses > 300 mg daily.

LoE:IV[b]

Poorly controlled epilepsy

» Ensure diagnosis of epilepsy and seizure type is confirmed and exclude imitators of epileptic seizures.
» Ask the patient, and if possible, a family member or primary care giver, about the following, as these factors can influence decisions regarding medicine therapy:
– Has the patient been adherent in taking the medication regularly for at least 2 weeks or more before the seizure? Ask about medicine dosage and frequency.
– If non-adherence has been established, ask for reasons contributing to non-adherence and offer guidance.
– Has the patient recently used some other medicine and/or herbal remedy (i.e., look for drug interactions, substance abuse or traditional medicine use).
– Is there a chance that alcohol is involved?
– If ≥ 1 of the above are present, address the problem/s but leave ASM therapy unchanged (unless dose adjustment is necessary

because of a drug interaction). Reassess the patient within 2 weeks.

REFERRAL

» People with epilepsy who have not responded to two trials of ASM monotherapy at therapeutic drug concentrations and require consideration of combination therapy.
» Epilepsy with unexplained neurological symptoms or signs.

Information on the seizures that should accompany each referral case:

» Number and frequency of seizures per month (or year).
» Date and time of most recent seizures.
» Detailed description of the seizures, including:
– Presence of an aura or warning signs
– what happens during the seizure? (give a step-by-step account)
– is the person conscious during the seizure?
– how long do the seizures last on average?
– what does the patient experience after the seizure?
– how long does this experience last?
» Is there a family history of seizures?
» What is the initial date of diagnosis?
» Is there evidence of alcohol use?
» Is there another medical condition, e.g. diabetes, HIV and what medication is used?
» What is the name and dosage of the ASM used to date?
» Does the person return regularly for repeat of medication?

14.7 HEADACHE AND FACIAL PAIN SYNDROMES

14.7.1 MIGRAINE

G43.0-3/G43.8-9

DESCRIPTION

A migraine is an episodic headache, usually located unilaterally and throbbing/ pulsating in nature, which may occur with or without an aura. Migraines are usually accompanied by nausea and/or vomiting, photophobia (sensitivity to light) and phonophobia (sensitivity to noise). There are several variants of migraine.

GENERAL MEASURES

Reassure patient that this is a benign condition.
Attempt to identify any precipitating factors or food triggers from the patient's history.

MEDICINE TREATMENT

Acute treatment

Initiate therapy during the migraine attack or at the onset of the headache.

Analgesia:

- Paracetamol, oral, 500 mg to1 g, 4 to 6 hourly as required (to a maximum of 4 g in 24 hours).
  - Maximum dose: 15 mg/kg/dose.

OR

- NSAID, e.g.:
- Ibuprofen, oral, 400 mg immediately then 8 hourly with meals, if needed.

For nausea:

- Metoclopramide, oral/IM, 10 mg 8 hourly, as required.

Prophylaxis (Z29.2)

Regular, daily, prophylactic therapy is advised if:

» attacks are frequent, i.e. more than 2–3 per month, or
» severe, causing a significant amount of disability, or
» attacks are long lasting, or
» patient poorly tolerates therapy for acute attacks.

- Amitriptyline, oral, 10–25 mg at bedtime. *LoE:IIIa[xlvi]*
  - Up-titrate dose to adequate clinical response.
  - Doses greater than 75 mg are seldom required.

OR *LoE:IIb[xlvii]*

Poor response or contraindication to amitriptyline:

- β-blocker, e.g.:
- Propranolol, oral, 40 mg 12 hourly.
  - Titrate dose to adequate response
  - Maximum dose: 120–240 mg daily. *LoE:IIIb[xlviii]*

REFERRAL

Inadequate response to treatment.

14.7.2 CLUSTER HEADACHE

G44.0

DESCRIPTION

Repetitive episodes of excruciating headache typically of short duration (up to 2 hours) in clusters for weeks to months at a time. Typically, the headache is of sudden onset, unilateral during the specific cluster, and quickly reaches a climax. Associated redness of the eye with lacrimation and rhinorrhoea occurs.

MEDICINE TREATMENT

- Oxygen inhalation may abort some episodes. *LoE:IIIb[xlix]*

Analgesics are ineffective.

To induce rapid remission in patients with episodic cluster headache:

- Corticosteroids (intermediate-acting) e.g.:
- Prednisone, oral, 40 mg daily for 5–10 days.
  - Tapering is not necessary when the above duration is used.

LoE:IVb[1]

Prophylaxis

- Verapamil, oral, 40–80 mg 12 hourly.

REFERRAL

Inadequate response to treatment.

14.7.3 TRIGEMINAL NEURALGIA

G50.0

See Section26.1.4: Management of neuropathic pain.

14.7.4 TENSION HEADACHE

G44.2

DESCRIPTION

Tension headaches are described as a tight band around the head and are generally worse in the afternoon. Usually occurs over the back of the head but may extend over the entire head.

GENERAL MEASURES

Consider use of relaxation techniques.
Exclude medication overuse headache (see Section14.5.5: Medication overuse headache).

MEDICINE TREATMENT

- Amitriptyline, oral, 10–75 mg at night.

REFERRAL

» Atypical pain and/or focal neurological signs and symptoms, suggestive of alternate diagnosis.
» Poor response to therapy.

14.7.5 MEDICATION OVERUSE HEADACHE

G44.4

DESCRIPTION

Medication overuse headache generally occurs for ≥ 15 days per month for more than 3 months and develops as a consequence of regular overuse of analgesics for acute pain-relief. The headache develops or markedly worsens during medication overuse, and usually, but not invariably, resolves after the overuse is stopped. LoE:IVb[ii]

GENERAL MEASURES

Stop all analgesics.
Counsel patient regarding the link between overuse of analgesics and the development of and/or worsening of the headache syndrome.
The headache usually resolves after the overuse is stopped but may transiently worsen.

MEDICINE TREATMENT

- Amitriptyline, oral, 10 mg at night. LoE:IIIb[iii]
  - Increase to a maximum of 75 mg at night.
  - May be used during withdrawal of acute or symptomatic headache treatment.

14.7.6 IDIOPATHIC INTRACRANIAL HYPERTENSION (PSEUDOTUMOUR CEREBRI)

G93.2

DESCRIPTION

Patients present with symptoms (chronic headache, visual disturbance or loss due to papilloedema and tinnitus) and signs (papilloedema) of raised intracranial pressure without structural intracranial abnormality and with normal CSF composition.

Diagnosis

All patients should have neuroimaging (CT scan).

» If this is normal, i.e. the absence of structural lesions or hydrocephalus, perform a lumbar puncture and measure intracranial pressure.
» Diagnosis is confirmed by the presence of raised CSF pressure > 20 cm H_20.

GENERAL MEASURES

Stop medicines associated with benign intracranial hypertension (e.g. doxycycline, corticosteroids, combined oral contraceptives).
Regular monitoring of visual fields is crucial.
Weight loss.
Repeated lumbar punctures with measurement of opening pressure (do lumbar puncture with patient in left lateral position).

Consider surgery if there is progression of visual defects, despite medical therapy, visual loss at onset, or severe papilloedema.

MEDICINE TREATMENT

Discuss all cases with a specialist.

For visual involvement, persistent headaches, or severe papilloedema:

- Acetazolamide, oral, 250 mg 12 hourly
  - Increase, as required, by 250 mg daily every week to the maximum tolerated dose (not exceeding 4 g daily).

OR

LoE:IIIb[iii]

- Furosemide, oral, 40 mg daily.

REFERRAL

» For neuro-imaging, if not available locally.
» Visual symptoms or deterioration of visual fields for opthalmology evaluation.
» Patients not responding to therapy or in need of surgical management.

14.8 INFECTIOUS AND PARASITIC CONDITIONS

14.8.1 MENINGITIS

A32.1† + (G01*)/A39.0† + (G01*)/G00.0-3/G00.8-9/G03.0-2/G03.8-9
**N. meningitidis*, *H. influenzae* Type B and listeriosis are notifiable medical conditions.

DIAGNOSIS

Computed tomography should be done before lumbar puncture in patients with:
» focal neurological signs,
» new seizures,
» papilloedema, or
» reduced level of consciousness.

In cases where lumbar puncture is delayed or cannot be done (e.g. uncontrolled significant bleeding tendency), commence empiric antibiotic therapy after taking samples for blood cultures. Attempt the lumbar puncture later, if possible.

GENERAL MEASURES

Observe patient closely with regular monitoring of vital signs and neurological state.
Pay close attention to hydration status.
Nurse patients in a quiet, semi-dark surrounding.
Repeated lumbar punctures are of no benefit in uncomplicated bacterial meningitis.

Prompt initiation of antibiotic therapy is associated with improved outcomes in patients with bacterial meningitis.

MEDICINE TREATMENT

All patients require sufficient analgesia:

- Paracetamol, oral, 500 mg to1 g, 4 to 6 hourly as required (to a maximum of 4 g in 24 hours).
  - Maximum dose: 15 mg/kg/dose.

AND/OR

- NSAID, e.g.:
- Ibuprofen, oral, 400 mg then 8 hourly with meals, if needed.

Severe pain:

- Tramadol, oral, 50–100 mg 4–6 hourly.
  - May be increased to a maximum daily dose of 400 mg.

Antibiotic therapy

Empiric therapy for bacterial meningitis, until sensitivity results are available:

- Ceftriaxone, W IV, 2 g 12 hourly for 10 days.

LoE:IIIb^{iv}

Adjunctive corticosteroids are not recommended as trials in low-middle income countries have not demonstrated benefit.

Meningococcal meningitis A39.0† + (G01*)

For confirmed meningococcal disease only:

- Benzylpenicillin (penicillin G), A IV, 20–24 MU daily in 4–6 divided doses for one week.

AND

Eradicate nasopharyngeal carriage with a single dose of ciprofloxacin 500 mg after completing course of benzylpenicillin. This is not required if the patient received an initial, pre-referral dose of ceftriaxone.

- Ciprofloxacin, W oral, 500 mg immediately as a single dose.

Severe penicillin allergy: (Z88.0)

- Meropenem, W IV, 2 g 8 hourly for 7 days.

LoE:IIIb^{iv}

Prophylaxis of contacts:

Only for close household contacts and for healthcare workers who resuscitate patients before they received appropriate treatment.

- Ciprofloxacin, W oral, 500 mg immediately as a single dose.

Pneumococcal meningitis G00.1

Conditions causing cerebrospinal fluid (CSF) leaks increase the risk for this type of infection, e.g. skull fractures, congenital defects, neurosurgery.

If sensitive to penicillin:

- Benzylpenicillin (penicillin G), A IV, 20–24 MU daily in 4–6 divided doses for 10 days.

If resistant to penicillin:

- Ceftriaxone, W IV, 2 g 12 hourly for at least 10 days.

Severe penicillin allergy: (Z88.0)

- Meropenem, W IV, 2 g 8 hourly for 10 days.

Note: Consult a microbiologist/infectious diseases specialist.

Haemophilus influenzae G00.0

- Ceftriaxone, W IV, 2 g 12 hourly for 10 days.

Severe penicillin allergy: (Z88.0)

- Meropenem, W IV, 2 g 8 hourly for 10 days.

Note: Consult a microbiologist/infectious diseases specialist.

***Listeria monocytogenes* meningitis** A32.1†

- Ampicillin, A IV, 3 g 6 hourly for 21 days. *LoE:IIIb*[iv]

AND

- Gentamicin, A IV, 5 mg/kg daily for 7 days (may be prolonged if response is poor). See Appendix II for guidance on prescribing.

Severe penicillin allergy: (Z88.0)
Consult a specialist.

REFERRAL

» For neuro-imaging: patients not responding or worsening in condition, i.e. decrease in consciousness and cranial nerve palsies, despite appropriate therapy. This is especially urgent in patients with tuberculous meningitis, who may develop hydrocephalus and require an urgent shunting procedure.
» Patients with shunts.

14.8.1.1 TUBERCULOUS MENINGITIS (TBM)

A17.0† + (G01*)

DIAGNOSIS

CSF findings are extremely variable. Generally, lymphocytes predominate, however, polymorphs predominate initially in about a third of patients.
Protein is usually > 1 g/L and glucose is usually low.

In cases where the differential diagnosis between bacterial and tuberculous meningitis is in doubt, lumbar puncture should be repeated 2–3 days later

while still on ceftriaxone. If the aetiology is bacterial, considerable improvement in CSF findings may be expected, but with untreated tuberculous meningitis, the cell counts and protein levels will be the same or higher as the original CSF findings; and the glucose level will be the same or lower.

MEDICINE TREATMENT

Treat with standard combination tuberculosis therapy according to National protocol and extend duration of therapy to 9 months (2 months intensive phase, 7 months continuation phase). See Section16.9: Tuberculosis, Pulmonary for details.

In HIV-negative individuals:
Corticosteroid use may be of benefit in reducing neurological deficit in patients with grade II to III disease (focal neurological disease, depressed levels of consciousness, or a Glasgow Coma Scale of 14 or less).

- Dexamethasone, IV, dosing as follows:

Weeks	Dosing regimen
Initial dose	0.3-0.4 mg/kg/day for 2 weeks.
Week 3	0.2 mg/kg daily.
Week 4	0.1 mg/kg daily.
Week 5 to 8	4 mg/day, tapering daily dose by 1 mg each week.

OR

- Corticosteroids (intermediate-acting) e.g.: *LoE:IIa*[lvii]
- Prednisone, oral, 60 mg daily for 2 weeks.
  - Then taper gradually over the next 6 weeks (see Appendix II for an example of a dose reduction regimen). *LoE:IVb*[lviii]

In people with HIV: *LoE:IIa*[lix]
Note: There is uncertainty whether the use of corticosteroids is beneficial in PLWH with TBM. *LoE:IIa*[lx]

14.8.1.2 CRYPTOCOCCAL MENINGITIS

GENERAL MEASURES

People living with HIV (see Section10.2.4: Cryptococcosis)
» In PWH the aim is to suppress the infection until immune restoration occurs with antiretroviral therapy.

HIV-negative patients
» In HIV-negative patients the aim is to cure the infection.

14.8.1.2.1 CRYPTOCOCCAL MENINGITIS, HIV-INFECTED

See Section10.2.4: Cryptococcosis.

14.8.1.2.2 CRYPTOCOCCAL MENINGITIS, HIV-NEGATIVE

B45.1 + (G02.1*)

MEDICINE TREATMENT

Initial therapy:

LoE:IIIb[lxi]

- Amphotericin B, IV, 1 mg/kg daily.
  - Ensure adequate hydration to minimise nephrotoxicity (See Appendix II for preventing, monitoring, and management of toxicity).
  - Duration of initial IV therapy:
    - Treat intravenously for 4 weeks, provided that there are no neurological complications and follow up CSF culture at 2 weeks is negative.
    - In patients with neurological complications or persistent positive culture: increase the initial phase of therapy to 6 weeks in consultation with a specialist.

AND

LoE:IIb[lxii]

- Fluconazole, oral, 800 mg daily for 2 weeks, followed by 400 mg daily for 2 months.

Maintenance therapy:

- Fluconazole, oral, 200 mg daily for a minimum of 1 year.

Follow all patients closely for relapses.

LoE:IVb[lxiii]

Therapeutic lumbar puncture:

This should be considered as the intracranial pressure is often elevated with a communicating hydrocephalus. See Section10.2.4: Cryptococcosis.

14.8.2 VIRAL MENINGOENCEPHALITIS

A86/B00.4† + (G05.1*)

DESCRIPTION

Patients present with headache, neck stiffness, and encephalitic symptoms which may include fever, personality or behavioural changes, hallucinations and seizures. Lumbar puncture typically shows mildly elevated protein, normal glucose and mild pleocytosis (< 500), mainly lymphocytes (early on polymorphs may predominate). Treatment for herpes simplex encephalitis should be commenced in all patients until this has been excluded (see below).

MEDICINE TREATMENT

Analgesia:

- Paracetamol, oral, 500 mg to1 g, 4 to 6 hourly as required (to a maximum of 4 g in 24 hours).

- Maximum dose: 15 mg/kg/dose.

AND/OR

- NSAID, e.g.:
- Ibuprofen, oral, 400 mg immediately then 8 hourly with meals, if needed.

LoE:IVb[lxiv]

OR

- Morphine, IV, to a total maximum dose of 10 mg (see Appendix II, for individual dosing and monitoring for response and toxicity).

Herpes simplex encephalitis

Clinical features are fever, change in behaviour and seizures, which may be either focal or generalised.

Evidence of mucocutaneous involvement is usually not present. Lumbar puncture shows the above features of viral meningoencephalitis. Evidence of encephalitis involving medial temporal lobe region on MRI/CT neuro-imaging or on EEG is strongly supportive of the diagnosis and positive HSV PCR test on CSF is diagnostic.

- Aciclovir, IV, 10 mg/kg 8 hourly for 14 days (21 days in immunocompromised patients).
  - Start therapy as early as possible, i.e. before results are available.
  - A negative herpes PCR usually excludes the diagnosis unless the specimen was taken within 72 hours of onset of symptoms, when false negatives have been described.

Treat seizures appropriately, see Section14.6: Epilepsy. *LoE:IIa*[lxv]

All suspected cases of herpes encephalitis should be discussed with a specialist.

REFERRAL

» For neuro-imaging: patients not responding or worsening in condition, i.e. decrease in consciousness and cranial nerve palsies, despite appropriate therapy.
» Patients with shunts.

14.8.3 MENINGOVASCULAR SYPHILIS (NEUROSYPHILIS)

A52.1 + (G01*)

DIAGNOSIS

Lumbar puncture typically shows lymphocytosis with mildly elevated protein and low/normal glucose.
Serum syphilis serology: a negative TPHA or FTA excludes the diagnosis; RPR may be negative in some cases.
CSF syphilis serology: a CSF VDRL positive result is highly specific for neurosyphilis but may be negative in approximately 50%. A negative CSF FTA-ABS excludes the diagnosis of neurosyphilis.

MEDICINE TREATMENT

- Benzylpenicillin (penicillin G), A IV, 20 MU daily in 4–6 divided doses for 10 days.

LoE:IVb

A serum RPR response (4-fold decline in titre) after 6 months is predictive of treatment success for neurosyphilis.

LoE:IIIb[ixvi]

Severe penicillin allergy: (Z88.0)
Refer for consideration of desensitisation and subsequent treatment with benzylpenicillin at a referral centre.

14.8.4 BRAIN ABSCESS

G06.0

DIAGNOSIS

Patient may present with focal neurological signs and signs of infection. Neurological signs may not always be prominent. Neuro-imaging usually confirms diagnosis. Patients may have concomitant infection of ears, paranasal sinuses or lower respiratory tract.

MEDICINE TREATMENT

Empiric antibiotic therapy

- Ceftriaxone, W IV, 2 g 12 hourly.

AND

- Metronidazole, A oral, 400 mg 8 hourly **or** IV, 500 mg 8 hourly.

Adjust according to antimicrobial sensitivity after surgical drainage.

REFERRAL
All, as patients require urgent neurosurgery opinion and treatment.

14.8.5 ANTIMICROBIAL USE IN PATIENTS WITH HEAD INJURIES
S02.10-11/ /S06.11/S06.21/S06.31/S06.41/S06.51/S06.61/S06.71/S06.81/S06.91/ S09.9

MEDICINE TREATMENT
Basal skull fractures
Antibiotic prophylaxis is not indicated.

Penetrating brain injuries
Antibiotics are given for therapy.

- Ceftriaxone, (W) IV, 2 g 12 hourly for 7 days. *LoE:IVb*

14.8.6 NEUROCYSTICERCOSIS
B69.0 + (G99.8*)

DIAGNOSIS
Patients may present with seizures and/or focal neurological deficit. Typical cystic lesions are seen on neuroimaging. Old, calcified lesions are inactive and do not require treatment.

GENERAL MEASURES
Health education.
Surgery for treatable ventricular blockage or spinal or intraocular cysts.

MEDICINE TREATMENT
For active or viable cysts only:

- Albendazole, oral, 12 hourly for 8 days.
  - ≥ 60 kg: 400 mg.
  - < 60 kg: 7.5 mg/kg to a maximum of 800 mg daily.

Note: Do not use in pregnancy due to teratogenicity.

AND *LoE:IIb[lxvii]*

- Corticosteroids (intermediate-acting) e.g.:
- Prednisone, oral, 60 mg daily for 8 days. *LoE:IVb[lxviii]*

Anticonvulsants, if required. See Section14.6: Epilepsy. *LoE:IIIb[lxix]*

REFERRAL
Uncontrolled seizures despite antiparasitic and anticonvulsant therapy.

14.9 MOVEMENT DISORDERS

DESCRIPTION
Abnormalities of movement/initiation of movement, divided into those with reduction of movement (hypokinesia or bradykinesia), or those with excessive movements (hyperkinesia).

14.9.1 PARKINSONISM, PRIMARY

14.9.1.1 IDIOPATHIC PARKINSON DISEASE
G20

DESCRIPTION
Parkinsonism is a syndrome characterised by tremor, rigidity, bradykinesia, and postural disturbances. It may be primary, i.e. Parkinson's disease; or secondary, i.e. drug-induced, or due to uncommon disorders that may initially resemble Parkinson's disease.

The objective of treatment is to:
» minimise disabling symptoms
» prevent complications and avoid serious drug-induced side effects

GENERAL MEASURES
General supportive therapy and advice about lifestyle modification, physiotherapy and occupational therapy.

MEDICINE TREATMENT
Note: Set therapeutic targets so that the patient is functioning as well as possible.

Bradykinesia, rigidity and postural disturbance:
- Carbidopa/levodopa, 25/100 mg (1 tablet), oral, 8 hourly, increase gradually according to clinical response.
  - Maximum dose of 200/800 mg daily (8 tablets).
  - Increase dose in consultation with a specialist.

REFERRAL
» Alternative diagnosis suspected (e.g. secondary Parkinsonism)
» No improvement or poor control with treatment.
» Increasing on/off phenomenon.
» Dyskinesias.

14.9.2 PARKINSONISM, SECONDARY

G21.0-4/G21.8-9/G24.0

DESCRIPTION

Secondary parkinsonism is caused by certain medicines (typical and atypical antipsychotics, anti-emetics, anticonvulsants (phenytoin, valproate) and SSRIs), nervous system disorders, or other systemic illnesses.

GENERAL MEASURES

Primary approach in drug-induced parkinsonism should be to stop the offending medicine if possible.

Refer to psychiatric services for review of antipsychotic treatment in patients requiring treatment for parkinsonism (see Section15.5.2: Schizophrenia spectrum disorders).

MEDICINE TREATMENT

Anticholinergics have a limited role in this setting and should be used with caution.

- Anticholinergic agent, e.g.:
- Orphenadrine, oral, 50 mg 8 hourly, increase gradually according to clinical response.
  - Usual dose: 150–250 mg daily.
  - Maximum dose: 400 mg daily.

LoE:IVb[lxx]

Note: Anticholinergic side effects are common and may be exacerbated by antipsychotics.

OR

- Carbidopa/levodopa, 25/100 mg (1 tablet), oral, 8 hourly.

Acute dystonic reaction: G24.0

Usually follows administration of dopamine-antagonistic drug, e.g. metoclopramide and phenothiazines.

- Anticholinergic agent, e.g.:
- Biperiden, IM/IV, 2 mg.
  - Repeat as necessary.

OR

- Promethazine, deep IM, 25–50 mg.
  - Decrease dose in the elderly to 25 mg.

LoE:IVb

14.9.3 ESSENTIAL TREMOR

G25.0

GENERAL MEASURES

Exclude and manage alternate causes, such as drugs, thyrotoxicosis and hyperadrenergic states. Occasionally a patient may present with essential

tremor and an additional neurological condition, which may make the diagnosis difficult.

MEDICINE TREATMENT

If tremor is severe and interfering with normal daily activity:

- Propranolol, oral,
  - Start at 20 mg daily and titrate as needed up to 80 mg 8 hourly.
  - Monitor for symptomatic bradycardia and/or hypotension. *LoE:IIIb*[lxxi]

14.9.4 CHOREA

G25.5

DESCRIPTION

Chorea is a hyperkinetic movement disorder characterized by involuntary brief, random, and irregular contractions conveying a feeling of restlessness to the observer. Chorea may be caused by hereditary neurodegenerative diseases; structural damage to deep brain structures; or be associated with autoimmune disorders, metabolic derangement, or certain drugs and hormones.

Aetiology is classified as:

» Rarer primary (idopathic or hereditary) – Huntington's chorea,; or
» More common secondary (acquired) – Sydenham's chorea, hemiballismus secondary to infarction, diabetes (hyperglycemia).

Symptoms include involuntary, random, irregular movements.

GENERAL MEASURES

Exclude potential underlying causes initially.
A careful history should include age of onset, time course (acute or insidious), past medical history, history of recent infection with group A beta-haemolytic streptococcus (GABHS), family history, and drug exposure.
Neuroimaging should be performed for new-onset cases, especially when asymmetric.
A variety of laboratory tests may be useful depending on the clinical context.

MEDICINE TREATMENT

Treat the underlying cause, if relevant.

First-generation antipsychotic agents (typical neuroleptics) may reduce chorea although there is little evidence to support their efficacy, and they are increasingly avoided due to increased risk of side effects.

- Haloperidol, oral, 0.75–5 mg 8–12 hourly. (Specialist consultation.)

REFERRAL
The need to refer may be based on the underlying cause and diagnostic workup.
Refer primary choreas for genetic counselling.

LoE:IVb

14.10 NEUROPATHY
See Section26.1.4: Management of neuropathic pain.

14.11 MYELOPATHY, ACUTE
G95.9

DESCRIPTION
Patients present with a sudden onset of paraparesis, with associated sensory loss, i.e. a sensory level may be found. Incontinence and autonomic instability may be present.

GENERAL MEASURES
Do cervical and thoracic spine films, with chest X-ray to exclude obstructive lesions before performing a lumbar puncture.

REFERRAL
All patients for urgent imaging.

14.12 MULTIPLE SCLEROSIS
G35

DESCRIPTION
A demyelinating disease of the central nervous system, characterised by relapsing and remitting episodes of unifocal or multifocal neurological dysfunction. Diagnosis is confirmed by imaging. The CSF may show oligoclonal bands and raised IgG index.
Recovery between acute flares of illness is common, although a general stepwise deterioration from baseline is usually found.

GENERAL MEASURES
Consult with neurologist for diagnosis and treatment.

REFERRAL
All patients.

14.13 MYASTHENIA GRAVIS

G70.0

DESCRIPTION

Myasthenia gravis is an autoimmune neuromuscular disorder characterised by fluctuating motor weakness involving ocular, bulbar, limb, and/or respiratory muscles.

The weakness is due to an antibody-mediated, immunologic attack directed at proteins in the postsynaptic membrane of the neuromuscular junction (acetylcholine receptors or receptor-associated proteins).

Consider this in patients with new onset weakness and fatiguability, particularly involving muscles of the eyes and those involved in swallowing.

MEDICINE TREATMENT

Discuss both diagnosis and treatment with a specialist.

- Pyridostigmine, oral, 60 mg 5 times daily.

LoE:IVb[lxxii]

Corticosteroids and azathioprine should only be used in consultation with a specialist.

14.14 OEDEMA, CEREBRAL

DESCRIPTION

Swelling of brain parenchymal tissue, due to vasogenic, cytotoxic and osmotic causes. Only the vasogenic causes, such as brain tumours and inflammation, respond to corticosteroids.

14.14.1 BRAIN OEDEMA DUE TO TUMOURS AND INFLAMMATION

G93.6

GENERAL MEASURES

Supportive management. See Section14.1.1: Stroke.

Treat the underlying cause. This is especially important where brain oedema is associated with systemic conditions, such as electrolyte disturbances and organ failure.

Patients with primary brain tumours or brain metastases should be considered for definitive treatment of the tumour, which includes surgery and/or radiotherapy.

MEDICINE TREATMENT

- Dexamethasone, IV, 4 mg 6 hourly, initially.

OR

- Betamethasone, oral/IV, 4 mg 6 hourly.
  - Discontinue if no response has occurred after 48 hours.
  - Taper dose according to response and duration of therapy.

14.14.2 BRAIN OEDEMA DUE TO TRAUMATIC INJURY

S06.10-11 + External Cause Code (V,W,X,Y)

GENERAL MEASURES

Refer patient for neurosurgical opinion, if indicated.
Supportive management. See Section14.1.1: Stroke.
Note: DVT prophylaxis with heparin may be contraindicated due to increased risk of bleeding.

The following measures should be used in patients with raised intracranial pressure:

» head elevation and position,
» airway and ventilation control,
» sedation and analgesia,
» control of fever,
» control of hypertension, and
» prevention of seizures.

Currently, no evidence supports the use of hyperventilation in this setting.

MEDICINE TREATMENT

For raised intracranial pressure, pending a definitive neurosurgical procedure only:

- Mannitol 15–25%, IV, 0.25–1 g/kg administered over 30–60 minutes.
  - Monitor neurological response and urine output.
  - Beware of hypovolaemia and electrolyte disturbances, especially hypokalaemia.

Note: Corticosteroids should not be used in this setting as they have a harmful effect.

14.15 SPINAL CORD INJURY, ACUTE

T09.3

GENERAL MEASURES

There is insufficient evidence for the use of high dose corticosteroids in this clinical setting.

For symptomatic management of:

» Constipation – see Section24.1.2: Constipation.
» Urinary retention – see Section7.3.6: Overactive bladder.
» High risk of pressure sores – See Primary Health Care STG & EML, Section5.19: Pressure ulcers/ sores.
» Spasticity – refer patients for multi-disciplinary rehabilitation.

REFERRAL

» Patients with cervical spinal cord injury for multidisciplinary rehabilitation to optimise cardiorespiratory and functional (including mental health) performance.

References:

[i] Tissue plasminogen activator: Emberson J, Lees KR, Lyden P, Blackwell L, Albers G, Bluhmki E, et al.; Stroke Thrombolysis Trialists' Collaborative Group. Effect of treatment delay, age, and stroke severity on the effects of intravenous thrombolysis with alteplase for acute ischaemic stroke: a meta-analysis of individual patient data from randomised trials. Lancet. 2014 Nov 29;384(9958):1929-35. https://www.ncbi.nlm.nih.gov/pubmed/25106063

Tissue plasminogen activator: Wardlaw JM, Murray V, Berge E, del Zoppo GJ. Thrombolysis for acute ischaemic stroke. Cochrane Database Syst Rev. 2014 Jul 29;(7):CD000213. https://www.ncbi.nlm.nih.gov/pubmed/25072528

Tissue plasminogen activator: Alteplase (window period 3 hours versus 4.5 hours): National Department of Health: Affordable Medicines, EDP-Adult Hospital level. Medicine Review: Alteplase – Window period for treating hyper acute ischaemic stroke, February 2018. http://www.health.gov.za/

Tissue plasminogen activator: National Department of Health. Essential Drugs Programme - Tertiary and Quaternary EML, December 2019. http://www.health.gov.za/

Tissue plasminogen activator (Alteplase, IV – window period): National Department of Health: Affordable Medicines, EDP-Adult Hospital level. Medicine Review: Alteplase for hyper acute ischaemic stroke, January 2018. http://www.health.gov.za/

Tissue plasminogen activator (Alteplase, IV – window period): Emberson J, Lees KR, Lyden P, Blackwell L, Albers G, Bluhmki E, et al.; Stroke Thrombolysis Trialists' Collaborative Group. Effect of treatment delay, age, and stroke severity on the effects of intravenous thrombolysis with alteplase for acute ischaemic stroke: a meta-analysis of individual patient data from randomised trials. Lancet. 2014 Nov 29;384(9958):1929-35 https://www.ncbi.nlm.nih.gov/pubmed/25106063

Tissue plasminogen activator: Nicola Logallo, Vojtech Novotny, Jörg Assmus, Christopher E Kvistad, Lars Alteheld, Ole Morten Rønning, Bente Thommessen,Karl-Friedrich Amthor, Hege Ihle-Hansen, Martin Kurz, Håkon Tobro, Kamaljit Kaur, Magdalena Stankiewicz, Maria Carlsson, Åse Morsund,Titto Idicula, Anne Hege Aamodt, Christian Lund, Halvor Næss, Ulrike Waje-Andreassen, Lars Thomassen. Tenecteplase versus alteplase for management of acute ischaemic stroke (NOR-TEST): a phase 3, randomised, open-label, blinded endpoint trial. Lancet Neurology 2017; 16: 781–88. https://www.ncbi.nlm.nih.gov/pubmed/28780236

Tissue plasminogen activator; Alteplase IV: South African Medicines Formulary, 14th Edition. Division of Clinical Pharmacology. University of Cape Town, 2022.

[ii] Aspirin, oral (acute stroke): Sandercock PA, Counsell C, Tseng MC, Cecconi E. Oral antiplatelet therapy for acute ischaemic stroke. Cochrane Database Syst Rev. 2014 Mar 26;(3):CD000029. https://www.ncbi.nlm.nih.gov/pubmed/24668137

Aspirin, oral (acute stroke): Rothwell PM, Algra A, Chen Z, Diener HC, Norrving B, Mehta Z. Effects of aspirin on risk and severity of early recurrent stroke after transient ischaemic attack and ischaemic stroke: time-course analysis of randomised trials. Lancet. 2016 Jul 23;388(10042):365-375. https://www.ncbi.nlm.nih.gov/pubmed/27209146

[iii] Aspirin: Sandercock PA, Counsell C, Tseng MC, Cecconi E. Oral antiplatelet therapy for acute ischaemic stroke. Cochrane Database Syst Rev. 2014 Mar 26;3:CD000029.http://www.ncbi.nlm.nih.gov/pubmed/24668137

[iv] Simvastatin 40 mg, oral (secondary prevention of ischaemic events): National Department of Health. Affordable Medicines, EDP-Primary Health Care. Cost-effectiveness analysis of high, intermediate, and low dose statins for the secondary prevention of cardiovascular disease, 31 January 2018. www.health.gov.za/

Simvastatin 40 mg, oral (secondary prevention of ischaemic events): Cholesterol Treatment Trialists' (CTT) Collaboration. Efficacy and safety of more intensive lowering of LDL cholesterol: a meta-analysis of data from 170 000 participants in 26 randomised trials. The Lancet 2010; 376(9753): 1670-81. https://www.ncbi.nlm.nih.gov/pubmed/21067804

Simvastatin 40 mg, oral (secondary prevention of ischaemic events): Naci H, Brugts JJ, Fleurence R, Ades A. Dose-comparative effects of different statins on serum lipid levels: a network meta-analysis of 256,827 individuals in 181 randomized controlled trials. European journal of preventive cardiology 2013; 20(4): 658-70. https://www.ncbi.nlm.nih.gov/pubmed/23529608

Simvastatin 40 mg, oral (secondary prevention of ischaemic events): Contract circular HP09-2016SD. http://www.health.gov.za/

[v] Atorvastatin 10 mg, oral (secondary prevention of ischaemic events – patients on protease inhibitors): Chastain DB, Stover KR, Riche DM. Evidence-based review of statin use in patients with HIV on antiretroviral therapy. J Clin Transl Endocrinol. 2017 Feb 22;8:6-14. https://www.ncbi.nlm.nih.gov/pubmed/29067253

Atorvastatin 10 mg, oral (secondary prevention of ischaemic events – patients on protease inhibitors): National Department of Health. Affordable Medicines, EDP-Primary Health Care. Cost-effectiveness analysis of high, intermediate, and low dose statins for the secondary prevention of cardiovascular disease, 31 January 2018. www.health.gov.za/

Atorvastatin 10 mg, oral (secondary prevention of ischaemic events – patients on protease inhibitors): Cholesterol Treatment Trialists' (CTT) Collaboration. Efficacy and safety of more intensive lowering of LDL cholesterol: a meta-analysis of data from 170 000 participants in 26 randomised trials. The Lancet 2010; 376(9753): 1670-81. https://www.ncbi.nlm.nih.gov/pubmed/21067804

Atorvastatin 10 mg, oral (secondary prevention of ischaemic events – patients on protease inhibitors): Naci H, Brugts JJ, Fleurence R, Ades A. Dose-comparative effects of different statins on serum lipid levels: a network meta-analysis of

256,827 individuals in 181 randomized controlled trials. European journal of preventive cardiology 2013; 20(4): 658-70. https://www.ncbi.nlm.nih.gov/pubmed/23529608

Atorvastatin 10 mg, oral (secondary prevention of ischaemic events – patients on protease inhibitors): Contract circular HP09-2016SD. http://www.health.gov.za/

Atorvastatin, oral (drug-drug interaction with protease inhibitors): University of Liverpool. HIV drug interaction database. https://www.hiv-druginteractions.org/

[vi] Simvastatin 40 mg, oral (amlodipine drug interaction): Lexicomp: Drug Interactions database. [Accessed 7 February 2018] Available at: https://www.uptodate.com/drug-interactions

[vii] High dose statins (management of adverse drug reactions): NICE: Cardiovascular disease: risk assessment and reduction, including lipid modification. Clinical guideline, 18 July 2014. www.nice.org.uk/guidance/cg181

[viii] Warfarin: Lansberg MG, O'Donnell MJ, Khatri P, Lang ES, Nguyen-Huynh MN, Schwartz NE, Sonnenberg FA, Schulman S, Vandvik PO, Spencer FA, Alonso-Coello P, Guyatt GH, Akl EA; American College of Chest Physicians. Antithrombotic and thrombolytic therapy for ischemic stroke: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest. 2012 Feb;141(2 Suppl):e601S-36S. http://www.ncbi.nlm.nih.gov/pubmed/22315273

[ix] Blood pressure management (acute stroke): Bath PM, Krishnan K. Interventions for deliberately altering blood pressure in acute stroke. Cochrane Database Syst Rev. 2014 Oct 28;(10):CD000039. https://www.ncbi.nlm.nih.gov/pubmed/25353321

[x] Long-acting calcium channel blocker/Thiazide diuretic: Bath PM, Krishnan K. Interventions for deliberately altering blood pressure in acute stroke. Cochrane Database Syst Rev. 2014 Oct 28;10:CD000039. http://www.ncbi.nlm.nih.gov/pubmed/25353321

Long-acting calcium channel blocker/Thiazide diuretic: He J, Zhang Y, Xu T, Zhao Q, Wang D, Chen CS, Tong W, Liu C, Xu T, Ju Z, Peng Y, Peng H, Li Q, Geng D, Zhang J, Li D, Zhang F, Guo L, Sun Y, Wang X, Cui Y, Li Y, Ma D, Yang G, Gao Y, Yuan X, Bazzano LA, Chen J; CATIS Investigators. Effects of immediate blood pressure reduction on death and major disability in patients with acute ischemic stroke: the CATIS randomized clinical trial. JAMA. 2014 Feb 5;311(5):479-89. http://www.ncbi.nlm.nih.gov/pubmed/24240777

[xi] Early BP Lowering (within 7 days of stroke onset): Wang H, Tang Y, Rong X, Li H, Pan R, Wang Y, Peng Y. Effects of early blood pressure lowering on early and long-term outcomes after acute stroke: an updated meta-analysis. PLoS One. 2014 May 22;9(5):e97917. https://www.ncbi.nlm.nih.gov/pubmed/24853087

[xii] Blood pressure management (24 hours after acute stroke): Powers WJ, Rabinstein AA, Ackerson T, Adeoye OM, Bambakidis NC, Becker K, et al. American Heart Association Stroke Council. 2018 Guidelines for the Early Management of Patients With Acute Ischemic Stroke: A Guideline for Healthcare Professionals From the American Heart Association/American Stroke Association. Stroke. 2018 Mar;49(3):e46-e110. https://www.ncbi.nlm.nih.gov/pubmed/29367334

[xiii] Warfarin: South African Medicines Formulary, 14th Edition. Division of Clinical Pharmacology. University of Cape Town, 2022.

[xiv] Aspirin: Thijs V, Lemmens R, Fieuws S. Network meta-analysis: simultaneous meta-analysis of common antiplatelet regimens after transient ischaemic attack or stroke. Eur Heart J. 2008 May;29(9):1086-92.http://www.ncbi.nlm.nih.gov/pubmed/18349026

[xv] Simvastatin 40 mg, oral (secondary prevention of ischaemic events): National Department of Health. Affordable Medicines, EDP-Primary Health Care. Cost-effectiveness analysis of high, intermediate, and low dose statins for the secondary prevention of cardiovascular disease, 31 January 2018. www.health.gov.za/

Simvastatin 40 mg, oral (secondary prevention of ischaemic events): Cholesterol Treatment Trialists' (CTT) Collaboration. Efficacy and safety of more intensive lowering of LDL cholesterol: a meta-analysis of data from 170 000 participants in 26 randomised trials. The Lancet 2010; 376(9753): 1670-81. https://www.ncbi.nlm.nih.gov/pubmed/21067804

Simvastatin 40 mg, oral (secondary prevention of ischaemic events): Naci H, Brugts JJ, Fleurence R, Ades A. Dose-comparative effects of different statins on serum lipid levels: a network meta-analysis of 256,827 individuals in 181 randomized controlled trials. European journal of preventive cardiology 2013; 20(4): 658-70. https://www.ncbi.nlm.nih.gov/pubmed/23529608

Simvastatin 40 mg, oral (secondary prevention of ischaemic events): Contract circular HP09-2016SD. http://www.health.gov.za/

[xvi] Atorvastatin 10 mg, oral (secondary prevention of ischaemic events – patients on protease inhibitors): Chastain DB, Stover KR, Riche DM. Evidence-based review of statin use in patients with HIV on antiretroviral therapy. J Clin Transl Endocrinol. 2017 Feb 22;8:6-14. https://www.ncbi.nlm.nih.gov/pubmed/29067253

Atorvastatin 10 mg, oral (secondary prevention of ischaemic events – patients on protease inhibitors): National Department of Health. Affordable Medicines, EDP-Primary Health Care. Cost-effectiveness analysis of high, intermediate, and low dose statins for the secondary prevention of cardiovascular disease, 31 January 2018. www.health.gov.za/

Atorvastatin 10 mg, oral (secondary prevention of ischaemic events – patients on protease inhibitors): Cholesterol Treatment Trialists' (CTT) Collaboration. Efficacy and safety of more intensive lowering of LDL cholesterol: a meta-analysis of data from 170 000 participants in 26 randomised trials. The Lancet 2010; 376(9753): 1670-81. https://www.ncbi.nlm.nih.gov/pubmed/21067804

Atorvastatin 10 mg, oral (secondary prevention of ischaemic events – patients on protease inhibitors): Naci H, Brugts JJ, Fleurence R, Ades A. Dose-comparative effects of different statins on serum lipid levels: a network meta-analysis of 256,827 individuals in 181 randomized controlled trials. European journal of preventive cardiology 2013; 20(4): 658-70. https://www.ncbi.nlm.nih.gov/pubmed/23529608

Atorvastatin 10 mg, oral (secondary prevention of ischaemic events – patients on protease inhibitors): Contract circular HP09-2016SD. http://www.health.gov.za/

Atorvastatin, oral (drug-drug interaction with protease inhibitors): University of Liverpool. HIV drug interaction database. https://www.hiv-druginteractions.org/

[xvii] Simvastatin 40 mg, oral (amlodipine drug interaction): Lexicomp: Drug Interactions database. [Accessed 7 February 2018] Available at: https://www.uptodate.com/drug-interactions

[xviii] High dose statins (management of adverse drug reactions): NICE: Cardiovascular disease: risk assessment and reduction, including lipid modification. Clinical guideline, 18 July 2014. www.nice.org.uk/guidance/cg181

[xix] Haloperidol (risk in dementia): Ma H, Huang Y, Cong Z, Wang Y, Jiang W, Gao S, Zhu G. The efficacy and safety of atypical antipsychotics for the treatment of dementia: a meta-analysis of randomized placebo-controlled trials. J Alzheimers Dis. 2014;42(3):915-37. https://www.ncbi.nlm.nih.gov/pubmed/25024323

Haloperidol (risk in dementia): National Institute for Health and Clinical Excellence. Guideline - Dementia: assessment, management and support for people living with dementia and their carers, 20 June 2018. https://www.nice.org.uk/guidance/ng97

Haloperidol (risk in dementia): South African Medicines Formulary, 14th Edition. Division of Clinical Pharmacology. University of Cape Town, 2022.

[xx] Thiamine oral/IM: Day E, Bentham PW, Callaghan R, Kuruvilla T, George S. Thiamine for prevention and treatment of Wernicke-Korsakoff Syndrome in people who abuse alcohol. Cochrane Database Syst Rev. 2013 Jul 1;7:CD004033. http://www.ncbi.nlm.nih.gov/pubmed/23818100

Thiamine oral/IM: National Department of Health, Essential Drugs Programme: Primary Health Care STGs and EML, 2018. http://www.health.gov.za/

[xxi] Epileptic Seizure (Definition): International League Against Epilepsy. Diagnostic Manual of the epilepsies. Epigraph Vol. 18 Issue 2, Fall 2016. https://www.epilepsydiagnosis.org

[xxii] Epileptic Seizure (Definition): International League Against Epilepsy. Epilepsy Imitators. https://www.epilepsydiagnosis.org/epilepsy-imitators.html

[xxiii] Epileptic Seizure (Definition): International League Against Epilepsy. Diagnostic Manual of the epilepsies. Epigraph Vol. 18 Issue 2, Fall 2016. https://www.epilepsydiagnosis.org

Scheffer IE, Berkovic S, Capovilla G, Connolly MB, French J, Guilhoto L. ILAE classification of epilepsies: Position paper of the ILAE Commission for Classification and Terminology. Epilepsia. 2017, 58 (4): 512-521.

[xxiv] Epileptic Seizure (Definition): Scheffer IE, Berkovic S, Capovilla G, Connolly MB, French J, Guilhoto L. ILAE classification of epilepsies: Position paper of the ILAE Commission for Classification and Terminology. Epilepsia. 2017, 58 (4): 512-521.

[xxv] Epileptic Seizure (Definition): International League Against Epilepsy. Diagnostic Manual of the epilepsies. Epigraph Vol. 18 Issue 2, Fall 2016. https://www.epilepsydiagnosis.org

[xxvi] Valproate – caution in pregnancy: European Medicines Agency - Pharmacovigilance Risk Assessment Committee. Assessment report EMA/198940/2018 - valproate exposure in pregnancy, 8 February 2018. http://www.ema.europa.eu/docs/en_GB/document_library/Referrals_document/Valproate_2017_31/Position_provided_by_CMDh/WC500250221.pdf

Valproate – caution in pregnancy: Meador K, Reynolds MW, Crean S, Fahrbach K, Probst C. Pregnancy outcomes in women with epilepsy: a systematic review and meta-analysis of published pregnancy registries and cohorts. Epilepsy Res. 2008 Sep;81(1):1-13. https://www.ncbi.nlm.nih.gov/pubmed/18565732

[xxvii] Epileptic Seizure (Recovery Position): Ausmed Adult Basic Life Support. https://www.ausmed.com/learn/articles/basic-life-support

[xxviii] Lorazepam IV/IM (status epilepticus): Prasad M, Krishnan PR, Sequeira R, Al-Roomi K. Anticonvulsant therapy for 2014 Sep 10;(9):CD003723. https://www.ncbi.nlm.nih.gov/pubmed/25207925

Lorazepam, IV/IM (status epilepticus): NICE. Epilepsies: diagnosis and management: Clinical guideline [CG137], published January 2012 and updated February 2016. https://www.nice.org.uk/guidance/cg137

Lorazepam, IV/IM (Rate of adminisration): University of Cape Town, Faculty of Health Sciences, Division of Clinical Pharmacology. (2024). South African Medicines Formulary (SAMF). SAMF website. https://samf-app.com

[xxix] Midazolam IM/IV: Silbergleit R, Durkalski V, Lowenstein D, Conwit R, Pancioli A, Palesch Y, Barsan W; NETT Investigators. Intramuscular versus intravenous therapy for prehospital status epilepticus. N Engl J Med. 2012 Feb 16;366(7):591-600. http://www.ncbi.nlm.nih.gov/pubmed/22335736

Midazolam IM/IV: NICE. Epilepsies: diagnosis and management: Clinical guideline [CG137], published January 2012 and updated February 2016. https://www.nice.org.uk/guidance/cg137

NICE. Epilepsies in children, young people and adults. April 2022 (Updated 2025) Available at https://www.nice.org.uk/guidance/ng217

[xxx] Diazepam IV (status epilepticus): Prasad M, Krishnan PR, Sequeira R, Al-Roomi K. Anticonvulsant therapy for 2014 Sep 10;(9):CD003723. https://www.ncbi.nlm.nih.gov/pubmed/25207925
Diazepam, IV (status epilepticus): NICE. Epilepsies: diagnosis and management: Clinical guideline [CG137], published January 2012 and updated February 2016. https://www.nice.org.uk/guidance/cg137
NICE. Epilepsies in children, young people and adults. April 2022 (Updated 2025) Available at https://www.nice.org.uk/guidance/ng217

[xxxi] Clonazepam IV (status epilepticus): Alvarez V, Lee JW, Drislane FW, Westover MB, Novy J, Dworetzky BA, Rossetti AO. Practice variability and efficacy of clonazepam, lorazepam, and midazolam in status epilepticus: A multicenter comparison. Epilepsia. 2015 Aug;56(8):1275-85. https://www.ncbi.nlm.nih.gov/pubmed/26140660
NICE. Epilepsies in children, young people and adults. April 2022 (Updated 2025) Available at https://www.nice.org.uk/guidance/ng217

[xxxii] Clonazepam (IM): D'Anto J, Beuchat I, Rossetti AO, Novy J. Clonazepam Loading Dose in Status Epilepticus: Is More Always Better? CNS Drugs. 2023 Jun;37(6):523-529. doi: 10.1007/s40263-023-01012-9. Epub 2023 Jun 8. PMID: 37291410; PMCID: PMC10276784.
NICE. Epilepsies in children, young people and adults. April 2022 (Updated 2025) Available at https://www.nice.org.uk/guidance/ng217

[xxxiii] Diazepam (Rectal): Glauser T, Shinnar S, Gloss D, Alldredge B, Arya R, Bainbridge J, Bare M, Bleck T, Dodson WE, Garrity L, Jagoda A, Lowenstein D, Pellock J, Riviello J, Sloan E, Treiman DM. Evidence-Based Guideline: Treatment of Convulsive Status Epilepticus in Children and Adults: Report of the Guideline Committee of the American Epilepsy Society. Epilepsy Curr. 2016 Jan-Feb;16(1):48-61. doi: 10.5698/1535-7597-16.1.48. PMID: 26900382; PMCID: PMC4749120.
Diazepam (Rectal): NICE. Epilepsies: diagnosis and management: Clinical guideline [CG137], published January 2012 and updated February 2016. https://www.nice.org.uk/guidance/cg137

[xxxiv] Phenytoin (avoid in poisoning): Shah AS, Eddleston M. Should phenytoin or barbiturates be used as second-line anticonvulsant therapy for toxicological seizures? Clin Toxicol (Phila). 2010 Oct;48(8):800-5. https://www.ncbi.nlm.nih.gov/pubmed/20923393
Phenytoin (avoid in poisoning): Chen HY, Albertson TE, Olson KR. Treatment of drug-induced seizures. Br J Clin Pharmacol. 2016 Mar;81(3):412-9. https://www.ncbi.nlm.nih.gov/pubmed/26174744

[xxxv] Levetiracetam (NGT): White R, Bradnam V. Handbook of Drug Administration via Enteral Feeding Tubes. Pharmaceutical Press. 2007

[xxxvi] Propofol, IV: Prabhakar H, Bindra A, Singh GP, Kalaivani M. Propofol versus thiopental sodium for the treatment of refractory status epilepticus. Cochrane Database Syst Rev. 2012 Aug 15;8:CD009202. http://www.ncbi.nlm.nih.gov/pubmed/22895985
Propofol, IV: NICE Clinical Guideline 137. The epilepsies: the diagnosis and management of the epilepsies in adults and children in primary and secondary care. Issued Jan 2012; modified Jan 2015. http://guidance.nice.org.uk/cg137

[xxxvii] Midazolam, IV: NICE Clinical Guideline 137. The epilepsies: the diagnosis and management of the epilepsies in adults and children in primary and secondary care. Issued Jan 2012; modified Jan 2015. http://guidance.nice.org.uk/cg137

[xxxviii] Epilepsy (Classification): Scheffer IE, Berkovic S, Capovilla G, Connolly MB, French J, Guilhoto L. ILAE classification of epilepsies: Position paper of the ILAE Commission for Classification and Terminology. Epilepsia. 2017, 58 (4): 512-521

[xxxix] Risk of congenital structural malformations and neurodevelopment harms: Pennell PB. Neurotherapeutics. 2016 and Medicines & Healthcare products Regulatory Agency safety leaflet).

[xl] Valproate – caution in pregnancy: European Medicines Agency - Pharmacovigilance Risk Assessment Committee. Assessment report EMA/198940/2018 - valproate exposure in pregnancy, 8 February 2018. http://www.ema.europa.eu/docs/en_GB/document_library/Referrals_document/Valproate_2017_31/Position_provided_by_CMDh/WC500250221.pdf
Valproate – caution in pregnancy: Meador K, Reynolds MW, Crean S, Fahrbach K, Probst C. Pregnancy outcomes in women with epilepsy: a systematic review and meta-analysis of published pregnancy registries and cohorts. Epilepsy Res. 2008 Sep;81(1):1-13. https://www.ncbi.nlm.nih.gov/pubmed/18565732

[xli] Anti-epileptic drug-drug interactions: National Department of Health, Essential Drugs Programme: Adult Hospital Level STGs and EML, 2019. http://www.health.gov.za/

[xlii] Epilepsy (Medicine Treatment): NICE. Epilepsies in children, young people and adults. April 2022 (Updated 2025) Available at https://www.nice.org.uk/guidance/ng217

[xliii] Lamotrigine, oral (dose titration): University of Cape Town, Faculty of Health Sciences, Division of Clinical Pharmacology. (2024). South African Medicines Formulary (SAMF). SAMF website. https://samf-app.com
Lamotrigine, oral (dose titration): South African Health Product Regulatory Authority. Approved Professional Information Package. Lamotrigine. Available at https://pi-pil-repository.sahpra.org.za/wp-content/uploads/2025/02/PI-Approved-Lamilepsy-31012025.pdf
Lamotrigine, oral (dose titration): Western Cape Department of Health. Lamotrigine dose titration protocol. 2019.

[xliv] Lamotrigine, drug-drug interactions with ART (adults): National Department of Health, Essential Drugs Programme: Adult Hospital Level STGs and EML, 2019. http://www.health.gov.za/
Lamotrigine, drug-drug interactions with ART (adults): National Department of Health. 2019 ART Clinical Guidelines for the Management of HIV in Adults, Pregnancy, Adolescents, Children, Infants and Neonates. https://www.knowledgehub.org.za/elibrary/2019-art-clinical-guidelines-management-hiv-adults-pregnancy-adolescents-children-infants

[xlv] Carbamazepine, oral: Gigli GL, Placidi F, Diomedi M, Maschio M, Silvestri G, Scalise A, Marciani MG. Nocturnal sleep and daytime somnolence in untreated patients with temporal lobe epilepsy: changes after treatment with controlled-release carbamazepine. Epilepsia. 1997 Jun;38(6):696-701. http://www.ncbi.nlm.nih.gov/pubmed/9186252

[xlvi] Migraine prophylaxis indications: Silberstein SD. Practice parameter: evidence-based guidelines for migraine headache (an evidence-based review): report of the Quality Standards Subcommittee of the American Academy of Neurology. Neurology. 2000 Sep 26;55(6):754-62. Erratum in: Neurology 2000 Jan 9;56(1):142. https://www.ncbi.nlm.nih.gov/pubmed/10993991

[xlvii] Amitriptyline, oral (migraine prophylaxis): National Department of Health: Affordable Medicines, EDP-Adult Hospital level. Medicine Review: Migraine prophylaxis, June 2018. http://www.health.gov.za/
Amitriptyline, oral (dose for migraine prophylaxis): Couch JR; Amitriptyline Versus Placebo Study Group. Amitriptyline in the prophylactic treatment of migraine and chronic daily headache. Headache. 2011 Jan;51(1):33-51. https://www.ncbi.nlm.nih.gov/pubmed/21070231
Amitriptyline, oral (dose for migraine prophylaxis): Loder E, Burch R, Rizzoli P. The 2012 AHS/AAN guidelines for prevention of episodic migraine: a summary and comparison with other recent clinical practice guidelines. Headache. 2012 Jun;52(6):930-45. https://www.ncbi.nlm.nih.gov/pubmed/22671714

[xlviii] Beta-blocker (migraine prophylaxis): National Department of Health: Affordable Medicines, EDP-Adult Hospital level. Medicine Review: Migraine prophylaxis, June 2018. http://www.health.gov.za/
Beta-blocker (migraine prophylaxis): Jackson JL, Cogbill E, Santana-Davila R, Eldredge C, Collier W, Gradall A, et al. A Comparative Effectiveness Meta-Analysis of Drugs for the Prophylaxis of Migraine Headache. PLoS ONE 2015;10(7):1-60. https://www.ncbi.nlm.nih.gov/pubmed/26172390

[xlix] Oxygen: Robbins MS, Starling AJ, Pringsheim TM, Becker WJ, Schwedt TJ. Treatment of Cluster Headache: The American Headache Society Evidence-Based Guidelines. Headache. 2016 Jul;56(7):1093-106. doi: 10.1111/head.12866. PMID: 27432623.

[l] Corticosteroids, oral (Therapeutic group): South African Medicines Formulary, 14th Edition. Division of Clinical Pharmacology. University of Cape Town, 2022.

[li] Medication overuse headache (classification): Headache Classification Committee of the International Headache Society (IHS).The International Classification of Headache Disorders, 3rd edition (beta version). Cephalalgia. 2013 Jul;33(9):629-808. https://www.ncbi.nlm.nih.gov/pubmed/23771276

[lii] Amitriptyline, oral: Descombes S, Brefel-Courbon C, Thalamas C, Albucher JF, Rascol O, Montastruc JL, Senard JM. Amitriptyline treatment in chronic drug-induced headache: a double-blind comparative pilot study. Headache. 2001 Feb;41(2):178-82. https://www.ncbi.nlm.nih.gov/pubmed/11251703

[liii] Acetazolamide oral: Piper RJ, Kalyvas AV, Young AM, Hughes MA, Jamjoom AA, Fouyas IP. Interventions for idiopathic intracranial hypertension. Cochrane Database Syst Rev. 2015 Aug 7;(8):CD003434. https://www.ncbi.nlm.nih.gov/pubmed/26250102
Acetazolamide, oral: South African Medicines Formulary, 14th Edition. Division of Clinical Pharmacology. University of Cape Town, 2022.
NORDIC Idiopathic Intracranial Hypertension Study Group Writing Committee; Wall M, McDermott MP, Kieburtz KD, Corbett JJ, Feldon SE, Friedman DI, Katz DM, Keltner JL, Schron EB, Kupersmith MJ. Effect of acetazolamide on visual function in patients with idiopathic intracranial hypertension and mild visual loss: the idiopathic intracranial hypertension treatment trial. JAMA. 2014 Apr 23-30;311(16):1641-51. doi: 10.1001/jama.2014.3312. PMID: 24756514; PMCID: PMC4362615.
ten Hove MW, Friedman DI, Patel AD, Irrcher I, Wall M, McDermott MP; NORDIC Idiopathic Intracranial Hypertension Study Group. Safety and Tolerability of Acetazolamide in the Idiopathic Intracranial Hypertension Treatment Trial. J Neuroophthalmol. 2016 Mar;36(1):13-9. doi: 10.1097/WNO.0000000000000322. PMID: 26587993.

[liv] Empiric antibiotic therapy:Proulx N, Fréchette D, Toye B, Chan J, Kravcik S. Delays in the administration of antibiotics are associated with mortality from adult acute bacterial meningitis. *QJM.* 2005 Apr;98(4):291-8. http://www.ncbi.nlm.nih.gov/pubmed/15760921
Empiric antibiotic therapy: Koster-Rasmussen R, Korshin A, Meyer CN. Antibiotic treatment delay and outcome in acute bacterial meningitis. J Infect. 2008 Dec;57(6):449-54. http://www.ncbi.nlm.nih.gov/pubmed/19000639

[lv] Meropenem, IV (severe penicillin allergy - bacterial meningitis): Gaeta F, Valluzzi RL, Alonzi C, Maggioletti M, Caruso C, Romano A. Tolerability of aztreonam and carbapenems in patients with IgE-mediated hypersensitivity to penicillins. J Allergy Clin Immunol. 2015 Apr;135(4):972-6. https://www.ncbi.nlm.nih.gov/pubmed/25457154

[lvi] Ampicillin, IV + gentamicin, IV (Listeriosis meningitis): Charlier C, Perrodeau É, Leclercq A, Cazenave B, Pilmis B, Henry B, Lopes A, Maury MM, Moura A, Goffinet F, Dieye HB, Thouvenot P, Ungeheuer MN, Tourdjman M, Goulet V,

de Valk H, Lortholary O, Ravaud P, Lecuit M; MONALISA study group. Clinical features and prognostic factors of listeriosis: the MONALISA national prospective cohort study. Lancet Infect Dis. 2017 May;17(5):510-519. https://www.ncbi.nlm.nih.gov/pubmed/28139432

Ampicillin, IV + gentamicin, IV (Listeriosis meningitis): Thønnings S, Knudsen JD, Schønheyder HC, Søgaard M, Arpi M, Gradel KO, Østergaard C; Danish Collaborative Bacteraemia Network (DACOBAN). Antibiotic treatment and mortality in patients with Listeria monocytogenes meningitis or bacteraemia. Clin Microbiol Infect. 2016 Aug;22(8):725-30. https://www.ncbi.nlm.nih.gov/pubmed/27345176

[lvii] Dexamethasone, IV : Prasad K, Singh MB. Corticosteroids for managing tuberculous meningitis. Cochrane Database Syst Rev. 2008 Jan 23;(1):CD002244. http://www.ncbi.nlm.nih.gov/pubmed/18254003

Dexamethasone, IV: Thwaites GE, Nguyen DB, Nguyen HD, Hoang TQ, Do TT, Nguyen TC, Nguyen QH, Nguyen TT, Nguyen NH, Nguyen TN, Nguyen NL, Nguyen HD, Vu NT, Cao HH, Tran TH, Pham PM, Nguyen TD, Stepniewska K, White NJ, Tran TH, Farrar JJ. Dexamethasone for the treatment of tuberculous meningitis in adolescents and adults. N Engl J Med. 2004 Oct 21;351(17):1741-51. https://www.ncbi.nlm.nih.gov/pubmed/15496623

[lviii] Corticosteroids, oral (Therapeutic group): South African Medicines Formulary, 14th Edition. Division of Clinical Pharmacology. University of Cape Town, 2022.

[lix] Prednisone, oral: Prasad K, Singh MB. Corticosteroids for managing tuberculous meningitis. Cochrane Database Syst Rev. 2008 Jan 23;(1):CD002244. http://www.ncbi.nlm.nih.gov/pubmed/18254003

[lx] Dexamethasone, IV (HIV-infected TBM): Prasad K, Singh MB. Corticosteroids for managing tuberculous meningitis. Cochrane Database Syst Rev. 2008 Jan 23;(1):CD002244. http://www.ncbi.nlm.nih.gov/pubmed/18254003

[lxi] Amphotericin B, IV (1 mg dose): Molloy SF, Kanyama C, Heyderman RS, Loyse A, Kouanfack C, Chanda D, Mfinanga S, Temfack E, Lakhi S, Lesikari S, Chan AK, Stone N, Kalata N, Karunaharan N, Gaskell K, Peirse M, Ellis J, Chawinga C, Lontsi S, Ndong JG, Bright P, Lupiya D, Chen T, Bradley J, Adams J, van der Horst C, van Oosterhout JJ, Sini V, Mapoure YN, Mwaba P, Bicanic T, Lalloo DG, Wang D, Hosseinipour MC, Lortholary O, Jaffar S, Harrison TS; ACTA Trial Study Team. Antifungal Combinations for Treatment of Cryptococcal Meningitis in Africa. N Engl J Med. 2018 Mar 15;378(11):1004-1017. https://www.ncbi.nlm.nih.gov/pubmed/29539274

[lxii] Amphotericin B, IV (duration of treatment in HIV-uninfected): Perfect JR, Dismukes WE, Dromer F, Goldman DL, Graybill JR, Hamill RJ, Harrison TS, Larsen RA, Lortholary O, Nguyen MH, Pappas PG, Powderly WG, Singh N, Sobel JD, Sorrell TC. Clinical practice guidelines for the management of cryptococcal disease: 2010 update by the infectious diseases society of America. Clin Infect Dis. 2010 Feb 1;50(3):291-322. https://www.ncbi.nlm.nih.gov/pubmed/20047480

[lxiii] Amphotericin B: Southern African HIV Clinicians Society: Guideline for the prevention, diagnosis and management of cryptococcal meningitis among HIV-infected persons:2013 update. S Afr J HIV Med 2013;14(2):76-86. [Online][Accessed 8March2015] http://www.sajhivmed.org.za/index.php/hivmed/article/view/82

Fluconazole: Southern African HIV Clinicians Society: Guideline for the prevention, diagnosis and management of cryptococcal meningitis among HIV-infected persons:2013 update. S Afr J HIV Med 2013;14(2):76-86. [Online][Accessed 8March2015] http://www.sajhivmed.org.za/index.php/hivmed/article/view/82

[lxiv] Ibuprofen: South African Medicines Formulary, 14th Edition. Division of Clinical Pharmacology. University of Cape Town, 2022.

[lxv] Aciclovir, IV (Herpes simplex encephalitis – duration of therapy): Tunkel AR, Glaser CA, Bloch KC, Sejvar JJ, Marra CM, Roos KL, Hartman BJ,Kaplan SL, Scheld WM, Whitley RJ; Infectious Diseases Society of America. The management of encephalitis: clinical practice guidelines by the Infectious Diseases Society of America. Clin Infect Dis. 2008 Aug 1;47(3):303-27. https://www.ncbi.nlm.nih.gov/pubmed/18582201

Aciclovir, IV (Herpes simplex encephalitis – duration of therapy): Sköldenberg B, Forsgren M, Alestig K, Bergström T, Burman L, Dahlqvist E, Forkman A, Frydén A, Lövgren K, Norlin K, et al. Acyclovir versus vidarabine in herpes simplex encephalitis. Randomised multicentre study in consecutive Swedish patients. Lancet. 1984 Sep 29;2(8405):707-11. https://www.ncbi.nlm.nih.gov/pubmed/6148470

Aciclovir, IV (Herpes simplex encephalitis – duration of therapy): Whitley RJ, Alford CA, Hirsch MS, Schooley RT, Luby JP, Aoki FY, Hanley D, Nahmias AJ, Soong SJ. Vidarabine versus acyclovir therapy in herpes simplex encephalitis. N Engl J Med. 1986 Jan 16;314(3):144-9. https://www.ncbi.nlm.nih.gov/pubmed/3001520

Aciclovir, IV (Herpes simplex encephalitis – duration of therapy): Solomon T, Michael BD, Smith PE, Sanderson F, Davies NW, Hart IJ, Holland M, Easton A, Buckley C, Kneen R, Beeching NJ; National Encephalitis Guidelines Development and Stakeholder Groups. Management of suspected viral encephalitis in adults--Association of British Neurologists and British Infection Association National Guidelines. J Infect. 2012 Apr;64(4):347-73. https://www.ncbi.nlm.nih.gov/pubmed/22120595

[lxvi] Serum RPR titre (predictor of treatment success): Marra CM, Maxwell CL, Tantalo LC, Sahi SK, Lukehart SA. Normalization of serum rapid plasma reagin titer predicts normalization of cerebrospinal fluid and clinical abnormalities after treatment of neurosyphilis. Clin Infect Dis. 2008 Oct 1;47(7):893-9. https://www.ncbi.nlm.nih.gov/pubmed/18715154

[lxvii] Albendazole: Abba K, Ramaratnam S, Ranganathan LN. Anthelmintics for people with neurocysticercosis. Cochrane Database Syst Rev. 2010 Jan 20;(1):CD000215. http://www.ncbi.nlm.nih.gov/pubmed/20091504

Albendazole: Garcia HH, Pretell EJ, Gilman RH, Martinez SM, Moulton LH, Del Brutto OH, Herrera G, Evans CA, Gonzalez AE; Cysticercosis Working Group in Peru. A trial of antiparasitic treatment to reduce the rate of seizures due to cerebral cysticercosis. N Engl J Med. 2004 Jan 15;350(3):249-58. http://www.ncbi.nlm.nih.gov/pubmed/14724304

[lxviii] Corticosteroids, oral (Therapeutic group): South African Medicines Formulary, 14th Edition. Division of Clinical Pharmacology. University of Cape Town, 2022.

[lxix] Prednisone: Vazquez VA, Sotelo J. The course of seizures after treatment for cerebral cysticercosis.*N Engl J Med.* 1992;327:696-701. http://www.ncbi.nlm.nih.gov/pubmed/1495522

[lxx] Orphenadrine: South African Medicines Formulary, 14th Edition. Division of Clinical Pharmacology. University of Cape Town, 2022.

[lxxi] Propranolol: Zesiewicz TA, Elble RJ, Louis ED, Gronseth GS, Ondo WG, Dewey RB Jr, Okun MS, Sullivan KL, Weiner WJ. Evidence-based guideline update: treatment of essential tremor: report of the Quality Standards subcommittee of the American Academy of Neurology. Neurology. 2011 Nov 8;77(19):1752-5. https://www.ncbi.nlm.nih.gov/pubmed/26678329

Zesiewicz TA, Kuo SH. Essential tremor. BMJ Clin Evid. 2015 Dec 15;2015. pii: 1206. https://www.ncbi.nlm.nih.gov/pubmed/26678329

Propanolol: Jefferson D, Jenner P, Marsden CD. Relationship between plasma propranolol concentration and relief of essential tremor. J NeurolNeurosurg Psychiatry. 1979 Sep;42(9):831-7. http://www.ncbi.nlm.nih.gov/pubmed/501384

[lxxii] Pyridostigmine: South African Medicines Formulary, 14th Edition. Division of Clinical Pharmacology. University of Cape Town, 2022.

CHAPTER 15
MENTAL HEALTH CONDITIONS AND SUBSTANCE MISUSE

MENTAL HEALTH CONDITIONS

Precepts of the Mental Health Care Act No. 17 of 2002 include:

» All patients with mental illness and/or severe to profound intellectual disability should receive mental health care as either Voluntary, Assisted or Involuntary Mental Health Care Users.
» All registered medical practitioners, professional nurses, psychologists, occupational therapists (OTs), and social workers whose training includes mental health are designated Mental Health Care Practitioners.
» Mental health care practitioners and heads of health establishments at PHC and Hospital Adults level must be familiar with MHCA Forms 01 – 13A, 14, 17, 22, 25, 26, 27, and 48.
» The South African Police Service (SAPS) have an obligation to protect, apprehend, and assist people with mental illness with transfer, to and between health establishments.

Meaning of selected terminology used in this chapter:

» **Psychoeducation** (psychological education) involves informing a patient and their family or support system about their illness and providing problem solving, communication, and assertiveness skills training. The goals are to enable understanding, self-care, crisis management, suicide prevention, and relapse prevention. Information on aetiological factors, signs and symptoms, early signs of relapse, treatment options, need for adherence to treatment, and long-term course and outcome should be provided with consideration of the individual and their family's culture, beliefs, and coping mechanisms. Myths and misconceptions regarding the illness and its treatment are identified and managed in a person-centred manner. Advice on managing difficult behaviour and emergency situations is provided, and stigma is dispelled.

  Psychoeducation may require several individual, family, or group sessions, depending on the complexity of the illness and the understanding of the problem by the individual and their family / support system. Involvement of a registered counsellor, occupational therapist, and/or social worker is advised.

  LoE:IVb[i]

» **Risk assessment** refers to a clinical judgement of the patient's potential for:
  - suicide or self-harm,
  - aggression or violence towards others,
  - being assaulted by others,
  - high risk sexual behaviour,

- severe self-neglect,
- being exploited,
- reputational damage,
- non-adherence to treatment,
- causing damage to property,
- poor physical health.

A risk assessment is performed by collecting information from the patient and relevant stakeholders which may include the person's family / support system, healthcare providers (including community health workers or social workers who have knowledge of the person's home), as well as past clinical and forensic history.

Close attention must be given to women in the perinatal period, people who care for others (e.g., parents, grandparents, teachers, and health and social care providers), and those with previous high-risk behaviour.

While the clinical judgement may not always be accurate, it should be justified by the available information. The clinical judgement serves to inform precautionary interventions, e.g. close clinical follow-up after hospital discharge with increased attention by the Ward-Based Outreach Team (WBOT), referral to social welfare / statutory services, advice regarding a protection order, and/or further psychoeducation.

A useful clinical guideline on how to conduct a risk assessment is available at: www.seslhd.health.nsw.gov.au/sites/default/files/documents/SESLHDGL%20082%20-%20%20Clinical%20Risk%20Assessment%20and%20Management%20-%20Mental%20Health1.pdf

15.1 AGGRESSIVE DISRUPTIVE BEHAVIOUR IN ADULTS

R45.1/45.4-8 + code(s) for underlying/comorbid condition(s)

DESCRIPTION

Agitation may escalate to overt aggression and often manifests with restlessness, pacing, and loud or demanding speech. Aggressive behaviour includes verbally abusive language, specific verbal threats, intimidating physical behaviour, and/or actual physical violence to self, others, or property. All agitation and aggression must be considered an emergency, and violence should be prevented wherever possible.

Causes for aggressive, disruptive behaviour include:

» **Physical:** acute medical illness, delirium and its causes (see Section 20.8: Delirium with perceptual disturbances), epilepsy (pre-, intra-, and post-ictal), intracerebral lesions, traumatic brain injury.
» **Psychiatric:** psychosis, mania, agitated depression, neurocognitive disorders

(e.g. dementias, old traumatic brain injury), developmental disorders (e.g. intellectual disability and autistic spectrum disorder), severe anxiety.

» **Substance misuse:** alcohol; cannabis; methaqualone (mandrax) intoxication or withdrawal; stimulant (cocaine, methamphetamine [tik], methcathinone [cat]) intoxication; benzodiazepine withdrawal.

» **Psychological factors:** high levels of impulsivity and antagonism, hypersensitivity to rejection or insult, poor frustration tolerance, and maladaptive coping skills may all contribute to aggression.

» **In pregnant women:** labour, obstetric complications, sepsis, organ failure as well as substances and mental disorders. (See Primary Health Care [PHC] Standard Treatment Guidelines [STGs] and Essential Medicines List [EML], Chapter 6 Obstetrics and Gynaecology, Section 6.9: Maternal mental health).

CAUTION

» **Do not assume that the aggression is due to mental illness or psychological factors.**

» Patients known with psychiatric conditions and/or intellectual disability often have co-morbid medical conditions, trauma, and substance misuse.

GENERAL MEASURES

» **Prepare, anticipate, and prevent**:
Be aware of high-risk patients e.g. those with previous violence, substance misuse, and State Patients on leave of absence. Have:
- a step-wise protocol to ensure safety of all patients and staff,
- clear roles for all staff members,
- a triage plan for early signs of aggression,
- available backup – hospital security and SAPS and EMS,
- a designated calming area – suitable for regular monitoring.

» **De-escalate and contain**:
- Be calm, confident, kind, and reassuring.
- Listen to the person.
- Maintain a submissive posture with open hands.
- Do NOT turn your back on the patient; avoid direct eye contact.
- Do NOT attempt to reason with the patient.
- Do NOT argue, confront delusions, or touch the patient.
- Set clear limits regarding behaviour.
- Take patient to quiet, calm area – do NOT leave unobserved.

» **Examine** for delirium, medical and other causes while calming the patient and after sedation.

» **Manual restraint:**
- May be necessary to administer medication.
- Manual restraint refers to interventions done with hands or bodies without the use of any device, to limit a user's movement of body or limb. It is sometimes called “holding”. Manual restraint must be respectful, controlled and kept to a

minimum. It should preferably be applied by personnel of the same sex as the patient.
- Report any injuries or death associated with the restraint to the Mental Health Review Board as well as the health facility quality assurance department.

LoE:IVb[ii]

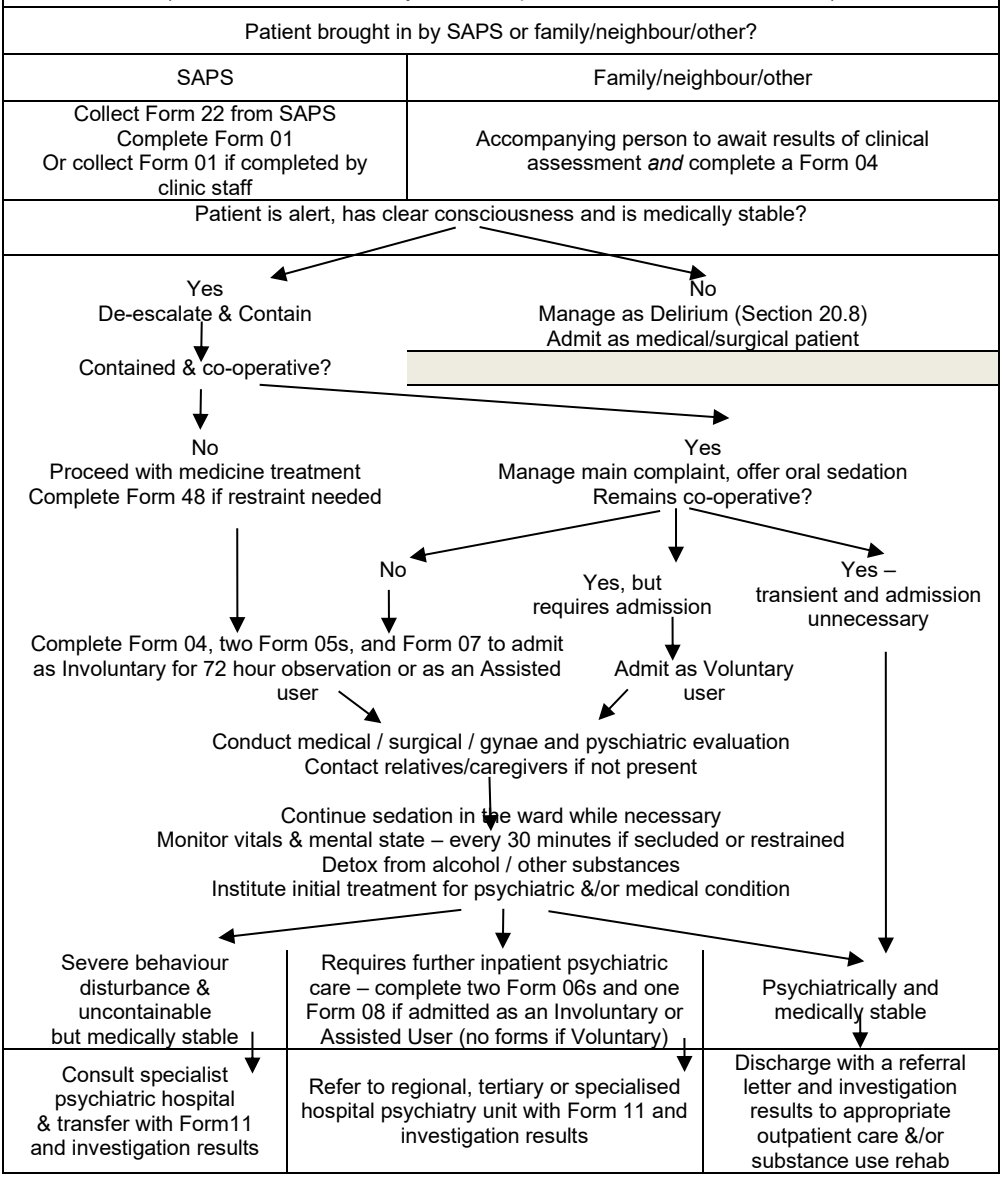
» **Mechanical restraint**:
- An emergency intervention in which an instrument or appliance is used to restrict movement of the body. See national policy guidelines on the use of mechanical restraint: https://knowledgehub.health.gov.za/system/files/elibdownloads/2023-04/Policy%252520guidelines%252520on%252520seclusion%252520and%252520restraint%252520of%252520mental%252520health%252520care%252520users%2525202012.pdf

LoE:IVb[iii]

- Only use if absolutely necessary to protect the patient and others for as short a time as possible, and as prescribed by a doctor.
- Document the type, sites, and duration of any restraints used.
- 15-minute monitoring: vital signs, mental state, restraint sites, and reasons for use.
- For people managed under the MHCA, complete a MHCA Form 48 (restraint register) and submit to the Mental Health Review Board, together with a report of any injuries or death associated with the restraint as well as to the health facility quality assurance department.

- **Pregnant women:**
  - Never leave unattended.
  - Avoid excessive force; gently nurse mother in a supported semi-seated position (not supine or prone), in an armchair or large beanbag if available.
  - Use restraint sparingly and with care.
- **Counsel the family/friend/patient escort regarding:**
  - Possible causes for the behaviour.
  - Reasons for restraints if used.
  - Importance of their continued support of the patient post-discharge.

Figure 15.1: Aggressive and Disruptive Behaviour in Adults
District Hospital Casualty & Ward guideline
(For PHC & CHC Casualty – see Chapter 15.1 in PHC STGs and EML)



for completion of 72-hour observation.		

MEDICINE TREATMENT

The goal of rapid tranquilisation is to calm the patient so that risk to self or others is minimised and manage the underlying condition.

CAUTION

» Rapid tranquillisation may cause cardiovascular collapse, respiratory depression, acute dystonic reactions, and neuroleptic malignant syndrome.
» Pregnant women, elderly, intellectually disabled, and those with comorbid medical conditions and/or substance use are at highest risk of serious adverse drug reactions.
» Late pregnancy: neonatal sedation or extra-pyramidal side effects may occur.
» **Write out single prescriptions and review between each prescription.**
» **Allow at least 30 – 60 minutes between prescriptions.**
» **An emergency trolley, airway, bag, oxygen, and intravenous line must be available for use if needed.**

LoE:IVb[iv]

» Monitor vital signs closely during and after medicine administration.
» Use the safest route of administration possible: The safest route of administration of benzodiazepines is oral followed by IM. IV route has the highest risk of respiratory depression and arrest.
» Do not use depot antipsychotic injections (e.g., flupenthixol decanoate or zuclopenthixol decanoate injections) for rapid tranquillisation.

Offer oral treatment:

If aggression is clearly caused by psychosis, or if pregnant, elderly/frail, or has significant risk for respiratory depression:

- Olanzapine, orodispersible tablet or IM, immediately:
  - Aggression clearly due to psychosis or if pregnant: 5–10 mg.
  - Elderly/frail, respiratory depression risk / medically unwell: 2.5–5 mg.
  - Repeat after 30–60 minutes if needed.

If cause of aggression unclear, non-pregnant, non-elderly/frail, and without significant risk for respiratory depression:

- Benzodiazepines, e.g.: *LoE:IIIb*[v]
- Lorazepam, oral, 0.5–2 mg immediately.

OR *LoE:IVb*[vi]

- Clonazepam, oral, 0.5–2 mg immediately.

OR *LoE:IVb*[vii]

- Diazepam, oral, 5–10 mg immediately.

OR *LoE:IVb*[viii]

- Midazolam, oral or buccal, 7.5–15 mg immediately.

LoE:IIIb[ix]

If there is an inadequate response to oral benzodiazepine (after 30–60 minutes), or where oral treatment is refused:

- Olanzapine, orodispersible tablet/IM, 5–10 mg immediately
  - Repeat after 30–60 minutes if needed.

Note: Repeated doses may result in excessive sedation.

LoE:IVb[x]

If there is an inadequate response to oral benzodiazepine with a history of intolerability to olanzapine (e.g. previous neuroleptic malignant syndrome):

- Lorazepam, IM, 0.5–2 mg immediately.

LoE:IIIb[xi]

OR

- Midazolam, IM, 7.5–15 mg immediately.

LoE:IVb[xii]

OR

- Clonazepam, IM, 0.5–2 mg immediately.

Note:

» To avoid inappropriate repeat dosing, allow at least 30 minutes for the oral/IM medication to take effect.

LoE:IIIb[xiii]

» Repeated IM doses of benzodiazepines may result in toxicity owing to accumulation.

» Lorazepam IM has slower onset of sedation than midazolam IM (32 vs 18 minutes) and longer duration of sedation (217 vs 82 minutes).

» Clonazepam oral or IM may be used if longer duration of sedation is required. Onset of action may be 30-60 minutes, with predicted maximum effect after 1-4 hours. There is an increased risk of accumulation due to its long half-life (18-50 hours). Allow at least 12 hours between repeat doses.

LoE:IVb[xiv]

LoE:IIb[xv]

To continue tranquilisation under specialist supervision in psychiatric wards:

- Zuclopenthixol acetate, IM, 50–150 mg every 2–3 days (specialist/specialist consultation).
  - Start with 50mg in neuroleptic-naïve patients.
  - Maximum dose: 400 mg over a two-week period.

LoE:IVb[xvi]

If alcohol use is suspected:

ADD

- Thiamine, oral, 300 mg immediately and daily for 14 days.

LoE:IIIb[xvii]

Monitor the patient:

» Nurse in recovery position – prevent aspiration. Nurse pregnant women in supported semi-seated position if possible or left lateral position, and not supine.

» Monitor pulse, respiratory rate, blood pressure, temperature every 5–10 minutes for the first hour, and then every 30 minutes until the patient is ambulatory. Use pulse oximeter if available.
» Pregnant women: monitor fetal heart rate as well as mother's vital signs.
» Continue monitoring once ambulatory, assessing for risk of falls and further injury (especially elderly and frail), re-emergence of aggression, and abscondment.
» If patient absconds – request assistance from SAPS with a MHCA Form 25.

Manage acute complications:
» *Respiratory depression:* if respiratory rate drops to <12 breaths/minute, or oxygen saturation <90% - give oxygen; be prepared to ventilate.
» *Circulatory collapse*: See Section 20.1: Cardiac arrest in adults.
» *Acute dystonia*: See PHC STGs and EML, Section 16.2.1: Extra-pyramidal side effects.
» *Neuroleptic Malignant Syndrome:* See PHC STGs and EML, Section 16.2.2: Neuroleptic malignant syndrome.

15.2 ANXIETY AND OBSESSIVE-COMPULSIVE DISORDERS

F40.0-2/F40.8-9/F41.0-3/F41.8-9/F42.0-9 + (F10.0-F19.9/R45.0-8/Z65.0-5/Z65.8-9/Z81.0-4/Z81.8)

DESCRIPTION

Anxiety is an emotional response to perceived or anticipated stress. It is diagnosed as a disorder when it is excessive or persistent and impacts daily functioning. Anxiety disorders often present with medically unexplained symptoms such as non-cardiac chest pain, abdominal discomfort, and neck and back muscle tension. However, anxiety symptoms may be caused by various medical conditions. In addition, medical conditions are commonly comorbid with anxiety disorders. They may exacerbate the symptoms, and the anxiety disorder may worsen the outcome of treatment of the medical condition.

Tobacco, alcohol, and other substance use are commonly associated with anxiety disorders. The substance use may be secondary to the disorder or causative or both. If caused by a substance, then an anxiety disorder due to the specific substance should be diagnosed.

Anxiety during pregnancy and the postnatal period may impact negatively on the mother's well-being and use of services, and is associated with poor psychological and neurodevelopmental outcomes in the child (See PHC STGs and EML, Chapter 6.9: Maternal mental health).

» **Psychological manifestations** of anxiety include panic symptoms, excessive worry, fear, mood changes, irritability, tearfulness, distress, and poor concentration.
» **Physical symptoms** include muscle tension, headache, abdominal cramps, nausea, palpitations, sweating, a choking feeling, shortness of breath, chest

pain, dizziness, numbness, and tingling of the hands and feet.
» **People with intellectual disability** may present with aggression, agitation, and demanding behaviour instead of anxiety.
» **Panic attacks** are abrupt surges of intense anxiety with prominent physical symptoms. They may occur in anxiety, mood, and psychotic disorders, and with alcohol and other substance misuse. They are a marker of increased severity of the primary disorder and may indicate a heightened risk of suicide.
» **Social phobia** (social anxiety disorder) is the fear of social interactions and usually starts in adolescence. Distorted thoughts are of perceived negative evaluation by others. Self-medication with alcohol or other substances is common and substance intoxication may be the presenting feature.
» **Obsessive thoughts and/or compulsive behaviour** are a core feature of obsessive-compulsive disorder but may also occur in other disorders, particularly tic disorders, autistic spectrum, and psychotic disorders. Themes of the distorted thoughts and compulsions include hygiene (cleaning), security, symmetry, sexual and taboo topics, fears of causing harm, perceived physical defects, hair-pulling, or hoarding.

GENERAL MEASURES

Most patients can be treated as outpatients, but some may need to be admitted for diagnostic clarification, containment in extreme distress, or if at high risk of suicide.
» Maintain patience and an empathic attitude.
» Screen for and manage:
  - causative and comorbid medical illness, e.g. thyroid disease, hyperparathyroidism, phaeochromocytoma, vestibular dysfunctions, epilepsy, and cardiac conditions, hypertension, COPD, asthma, inflammatory bowel disease, GORD.
  - substance misuse, e.g. caffeine, nicotine, alcohol, analgesics, amphetamines and cocaine.
  - psychosocial stressors, especially in people with intellectual and other disabilities.
» Psychoeducate the patient and family (with patient's permission).
» Refer to registered counsellors and local support groups. Provide links to self-help literature, websites or groups, e.g. South African Depression and Anxiety Group (SADAG - www.sadag.org).

MEDICINE TREATMENT

Indicated where symptoms interfere with normal functions of daily living.

» Offer a choice of psychotherapy (if available) or medication and monitor response. Note: where there is concomitant drug/alcohol dependence or a comorbid major depressive episode, an antidepressant may be more appropriate than psychotherapy.
» Review every 2–4 weeks for 3 months, then 3–6 monthly.
» Partial response: combine medication with psychotherapy.
» If effective, continue for at least 12 months to prevent relapse.

- Selective serotonin reuptake inhibitor (SSRI), e.g.:
- Fluoxetine, oral.
  - Initiate at 20 mg alternate days for 2 weeks.
  - Increase to 20 mg daily after 2–4 weeks.
  - Delay dosage increase if increased agitation / panic symptoms occur.
  - If partial response, increase to 40 mg daily.

LoE:Ib[xviii]

<u>If fluoxetine is poorly tolerated:</u>

- Alternative SSRI e.g.:
- Citalopram, oral.
  - Initiate at 10 mg daily for the 1st week.
  - Then increase to 20 mg daily.
  - If partial response, increase to 40 mg daily (except in cardiac disease or if >65 years of age).

LoE:Ib[xix]

CAUTION - SSRIs

SSRIs (e.g. fluoxetine, citalopram) may cause agitation initially. This typically resolves within 2-4 weeks.

LoE:IVb[xx]

Ask about suicidal ideation in all patients, particularly adolescents and young adults (PHC STGs and EML, Section 16.7: Suicide risk assessment). If suicidal ideation present, refer before initiating SSRI. Once started, monitor closely for clinical worsening, suicidality, or unusual changes in behaviour. Advise families and caregivers of the need for close observation and refer as required.

Note: Continue treatment for a minimum of 12 months. Consider slowly tapering and stopping treatment only if patient has had no/minimal symptoms and has been able to carry out routine daily activities.

Prolong treatment if any of the following are present:

» Previous episode/s of anxiety (extend treatment to at least 3 years).
» Any of the following: onset in adolescence, severe anxiety, suicidal attempt, sudden onset of symptoms, family history of bipolar disorder (extend treatment to at least 3 years).
» ≥3 previous episodes of anxiety (advise lifelong treatment).

LoE:IIIb[xxi]

<u>For short term use only in severe acute distress:</u>

- Benzodiazepines, e.g.:

LoE:IVb[xxii]

- Diazepam, oral, 2.5–5 mg as a single dose.
  - Repeat 8 hourly, if required to a maximum of 30 mg daily (in divided doses).
  - Half the dose in the elderly or debilitated.
  - Duration of therapy: up to 2 weeks, taper off to zero within 6 weeks.
  - Commence definitive treatment with psychotherapy/SSRI treatment.

CAUTION - BENZODIAZEPINES

» Associated with cognitive impairment – reversible with short-term use and irreversible with long-term use.
» Elderly are at risk of over-sedation, falls and hip fractures.
» Dependence may occur after only a few weeks of treatment.
» Prescribe for as short a period of time as possible to achieve desired effect.
» Warn patient not to drive or operate machinery when used short-term.
» Avoid use in people at high risk of addiction, e.g. personality disorders and those with previous or other substance misuse.

LoE:IVb[xxiii]

PREGNANCY AND BREASTFEEDING

» SSRI treatment of depression in pregnancy is associated with improved symptoms in the mother and better emotional and psychological development of the child. Benefit is greater with increasing illness severity. Effect of SSRIs on anxiety in pregnancy is less clear.
» Lack of matched case-control studies mean harms of treatment are unclear.
» If stable on an SSRI, do not stop – discuss risk/benefit with mother.
» Index presentations: offer counselling, psychotherapy; discuss risk/benefit of SSRIs.
» Refer social worker to explore social and financial support systems.
» Avoid fluoxetine due to long half-life and relatively high concentration in breastmilk. Consider citalopram as alternative
» All antidepressants: possible increased risk of miscarriage, transient neonatal symptoms (jitteriness, irritability), and persistent pulmonary hypertension of the newborn.
» Avoid benzodiazepines – some association with neurodevelopmental delay in the child; neonatal sedation if used late in pregnancy.

LoE:IVb[xxiv]

REFERRAL

» High suicide risk
» Severe symptoms with marked functional impairment.
» Co-morbid severe psychiatric or medical conditions.
» Poor response to treatment.

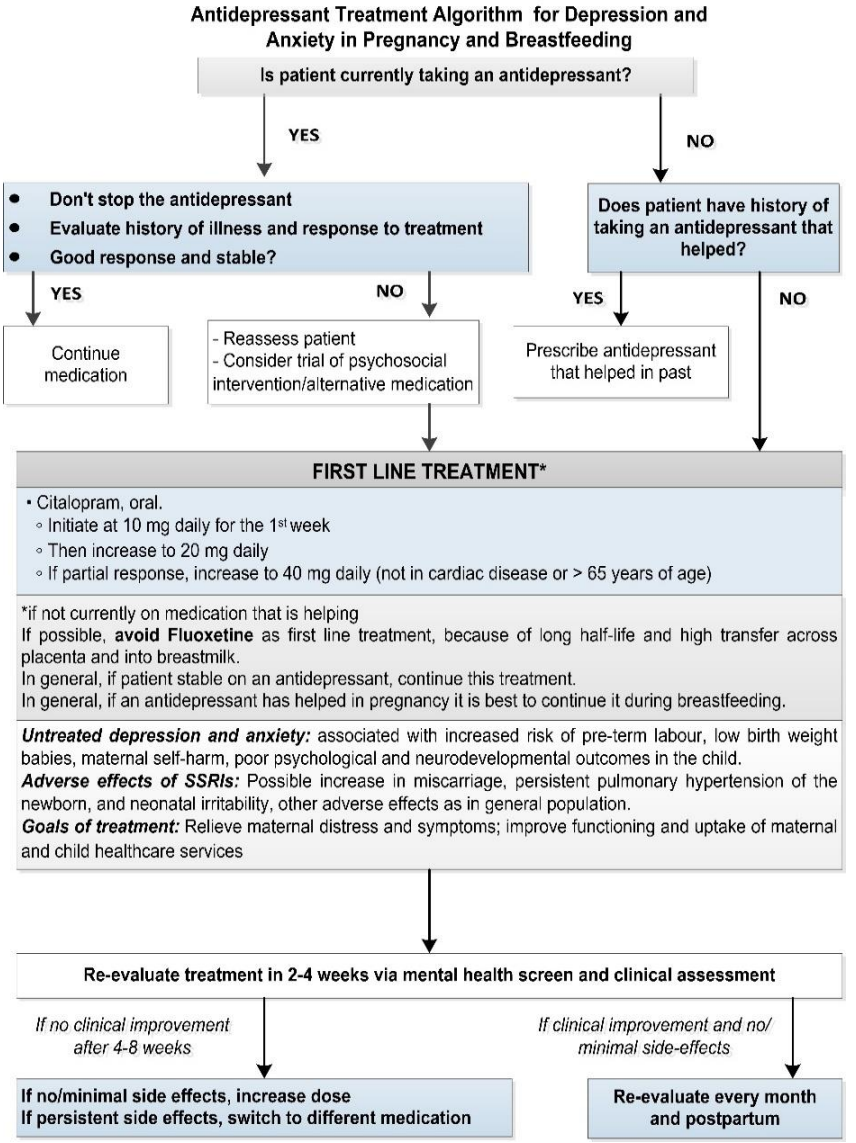


Figure 15.2: Antidepressant treatment algorithm for depression and anxiety in pregnancy and breastfeeding.
Adapted from the MCPAP for Moms Perinatal Depression Toolkit funded by the Massachusetts Department of Mental Health. Original Authors: Byatt N., Biebel K., Mittal L., Lundquist R., Freeman M., & Cohen L., Moore Simas T.

15.3 MOOD DISORDERS

15.3.1 DEPRESSIVE DISORDERS

F32.0-3/F32.8-9/F33.0-4/F33.8-9/F34.1 + (F10.0-F19.9/R45.0-8/Z65.0-5/Z65.8-9/Z81.0-4/Z81.8)

DESCRIPTION

Depressive disorders may occur as single or recurrent episodes, as a chronic, persistent low mood, or a combination of the two. Depressive disorders differ from bipolar disorder, in that there is no history of manic, hypomanic, or mixed episodes.

Depressive disorders cause significant impairment in social and occupational functioning, and may result in unemployment, poor self-care, neglect of dependent children, and suicide. They may be comorbid with, or secondary to, other medical illness or substance use. Depression impacts negatively on comorbid conditions, with increased pain, disability, and poorer treatment outcomes.

Depression is characterised by a low mood and/or a reduced capacity to enjoy life. However, it is often not recognised by the sufferer or clinician. It may be regarded as a normal emotional state or it may be unacceptable to the sufferer due to stigma. Thus, associated symptoms may be the presenting complaint rather than the low mood. Symptoms may also be masked in the interview setting. It is important to have a high degree of suspicion and to elicit symptoms, degree of impaired function, and suicide risk with care.

» In general, insomnia and loss of energy are the most common presenting complaints. In African cultures, somatic symptoms (bodily aches and pains) and rumination ('thinking too much') may predominate.
» The presence of mood, psychological, and cognitive symptoms help to differentiate between depression and normal sadness following a loss, or the loss of appetite and energy associated with a medical condition.
» Psychotic symptoms (delusions, hallucinations, or thought disorder) are usually mood congruent and indicate marked severity and a high risk to self or others.

Depression during pregnancy and the postnatal period is associated with preterm delivery, low-birth weight babies, poor maternal self-care, impaired mother-infant engagement, and poor psychological and neurodevelopmental outcomes in the child. Risk of negative impact is increased depending on severity (See PHC STGs and EML, Chapter 6.9: Maternal mental health).

GENERAL MEASURES

» Maintain an empathic and concerned attitude.
» Discuss uncertainty with a specialist at any point in the care pathway.
» Assess severity of the condition and suicide risk. See PHC STGs and EML Section 16.7: Suicide risk assessment.
» Exclude and optimise treatment of underlying and/or comorbid medical conditions (e.g. hypothyroidism, anaemia, HIV/AIDS, TB, cancers, diabetes).

» Screen for, and manage, underlying or comorbid substance use, e.g. nicotine, alcohol, over the counter analgesics, benzodiazepines.
» Screen for bipolar disorder and comorbid psychiatric disorders – refer for specialist assessment.
» Explore and address psychosocial stressors:
  - Stress management / coping skills – refer to registered counsellors, social worker, and/or occupational therapy.
  - Relationship and family issues – refer to social worker, registered counsellors, Non-Governmental Organisation (NGO) counselling, e.g. FAMSA (www.famsa.org.za).
  - If abuse, intimate partner, or other violence is evident, refer to a social worker.
» Provide self-help literature, where available, and refer to local support groups, e.g. SADAG (www.sadag.org).

MEDICINE TREATMENT

» Offer choice of psychotherapy (if available) or medication.
» Antidepressants take 4–6 weeks to achieve their maximum effect. There is little evidence to support combination medicine treatment.
» Tricyclic antidepressants (TCA) and selective serotonin reuptake inhibitors (SSRIs) are of equal efficacy.
» Electroconvulsive therapy (ECT) (specialist administered) is indicated under specific circumstances, e.g. severe depression, in pregnancy.
» The choice of therapy is guided by comorbid states, risk of overdose, and patient response.
» Refer to occupational therapy if available for vocational rehabilitation.

CAUTION - ANTIDEPRESSANTS

» SSRIs (e.g. fluoxetine, citalopram) may cause agitation and an increased suicide risk during the first 2–4 weeks.
» Once started, monitor closely for clinical worsening, suicidality, or unusual changes in behaviour. Advise families and caregivers of the need for close observation and refer as required.
» TCAs can be fatal in overdose. Prescription requires a risk assessment of the patient and others in their household, especially adolescents. See Section 19.6.1: Tricyclic antidepressant poisoning.
» Avoid TCAs in the elderly and in patients with heart disease, urinary retention, glaucoma, and epilepsy.
» Do not prescribe antidepressants to a patient with bipolar disorder without consultation, as they may precipitate a manic episode.
» Be aware of interactions between antidepressants and other agents (e.g. other medicines, St John's Wort or traditional African medicine).

PREGNANCY AND BREASTFEEDING

» SSRI treatment of depression in pregnancy is associated with improved symptoms in the mother and better emotional and psychological development of the child. Benefit is greater with increasing illness severity. Effect of SSRIs in pregnancy on anxiety is less clear.
» Lack of matched case-control studies mean harms of treatment are unclear.
» If stable on an SSRI, do not stop – discuss risk/benefit with mother.
» Index presentations: offer counselling and psychotherapy; discuss risk/benefit of SSRIs.
» Refer social worker to explore social and financial support systems.
» Avoid fluoxetine due to long half-life and relatively high concentration in breastmilk. Consider citalopram as alternative.
» All antidepressants: possible increased risk of miscarriage, transient neonatal symptoms (jitteriness, irritability), and persistent pulmonary hypertension of the newborn.
» Avoid benzodiazepines – some association with neurodevelopmental delay in the child; neonatal sedation if used late in pregnancy.

LoE:IVb[xxv]

- Selective serotonin reuptake inhibitor (SSRI), e.g.:
- Fluoxetine, oral.
  - Initiate at 20 mg alternate days for 2–4 weeks.
  - Thereafter, increase to 20 mg daily. Delay dosage increase if agitation/panic symptoms, suicidal ideation occur.
  - Reassess response after 4–6 weeks.
  - If partial response: increase to 40 mg daily and/or augment with psychotherapy.
  - If no response: consult with specialist (re-evaluate diagnosis, repeat general measures, prescribe alternative SSRI, psychotherapy, or ECT).

<u>If fluoxetine is poorly tolerated:</u>

- Alternative SSRI e.g.:
- Citalopram, oral.
  - Initiate at 10 mg daily for the 1st week.
  - Then increase to 20 mg daily.
  - If partial response: increase to 40 mg daily (except in cardiac disease and >65 years) and/or augment with psychotherapy.
  - If no response: consult with specialist (re-evaluate diagnosis, repeat general measures, prescribe alternative SSRI, psychotherapy, or ECT).

LoE:Ib[xxvi]

<u>If a sedating antidepressant is required:</u>

- Amitriptyline, oral, at bedtime.
  - Initial dose: 25 mg per day.
  - Increase by 25 mg per day at 3 to 5-day intervals.
  - Maximum dose: 150 mg per day.
  - If no response: discuss with specialist (re-evaluate diagnosis, repeat general measures, prescribe alternative SSRI, psychotherapy, or ECT).

LoE:IVb[xxvii]

Treatment duration
Continue for a minimum of 9 months. Consider stopping only if patient has had no/minimal symptoms and can carry out routine daily activities. Taper medicine slowly to avoid discontinuation symptoms; reinstitute if there is a recurrence.

Prolong treatment if:
» Concomitant generalised anxiety disorder (extend treatment to at least 1 year).
» Previous episode/s of depression (extend treatment to at least 3 years).
» Any of: severe depression, suicidal attempt, sudden onset of symptoms, family history of bipolar disorder (extend treatment to at least 3 years).
» If ≥3 episodes of depression, advise lifelong treatment. *LoE:IIb*[xxviii]

REFERRAL
» Inadequate response to treatment.
» High suicide risk.
» Psychotic features.

15.3.2 BIPOLAR AND RELATED DISORDERS
F06.3/F30.0-2/F30.8-9/F31.0-9/F34.0/F34.8-9/F38.0/F39 + (F10.0-F19.9/R45.0-8/Z65.0-5/Z65.8-9/Z81.0-4/Z81.8)

DESCRIPTION
Bipolar disorder (BD) is a heterogenous illness, with high overlap in genetic risk with depression and schizophrenia. It usually follows a chronic, relapsing course, commonly starting in youth. The goal of care is euthymia and optimal functioning according to the person's ability.

BD may present with:
» an episode of depression, hypomania, mania or mixed mood symptoms.
» psychosis.
» treatment resistant depression and/or anxiety.
» consequences of disturbed behaviour and/or comorbid substance use.
» depression in women; men are more likely to present with disruptive behaviour.

Diagnostic requirements include, over the lifetime course:
» Bipolar I disorder (BD I): an episode of mania
» Bipolar II disorder (BD II): an episode of hypomania and depression.
» Other specified BD (BD OS): symptoms of BD plus clinical distress and/or functional impairment but full Diagnostic and Statistical Manual criteria are not met.
» BD due to another medical condition: direct physiological cause for the bipolar symptoms from another illness, e.g. right-sided cortical or sub-cortical lesions.

Bipolar disorder during pregnancy and the post-natal period is associated with pre-eclampsia, preterm delivery, and low-birth weight babies. Risk of relapse is high, especially postpartum. Psychotic episodes may be dangerous to mother, baby, or others. (See PHC STGs and EML, Chapter 6.9: Maternal mental health.)

GENERAL MEASURES

Assess and manage **in consultation with a psychiatrist.**
Risk to self and others is high in BD and unpredictable – repeated risk assessments and a biopsychosocial approach to care is recommended.

Acute management

» Mania, severe depression, and psychosis require urgent hospitalisation in a psychiatric unit, often as an Assisted or Involuntary MHCU.
» Investigate for causative medical conditions, medications, substances.
» Optimise management of comorbid medical illness and substance use.
» Stabilise the immediate mood; electroconvulsive therapy may be required.
» Commence long-term treatment strategy.
» Avoid premature discharge and ensure continuity of care post-discharge.

Long-term management

» Individualise management according to course of illness, cognitive functioning, insight and judgement, and social circumstances.
» Assertive nursing with adherence monitoring is required.
» Screen for and manage comorbid medical illness (thyroid disease, HIV/AIDS, cardiovascular and pulmonary disease, epilepsy, diabetes, obesity).
» Screen for, and manage, substance use.
» Psycho-educate patient, family, and carers on the nature of the illness, need for continued treatment, how to self-monitor, early signs of relapse, and need for structure and routine.
» Refer to support groups e.g. SADAG (www.SADAG.org) or South African Federation For Mental Health (www.SAFMH.org.za).
» Refer to occupational therapy, if available, for insight, motivation, and vocational rehabilitation.
» Delay important decisions until full recovery from an acute episode; a custodian/ curatorship / power of attorney may be required.
» Refer to social worker for placement in a residential home, day care, or sheltered employment/workshop as needed.

Women of child-bearing potential (See PHC STGs and EML, Chapter 6.9: Maternal mental health).

» Advise family planning – psychoeducate regarding the need to plan pregnancy and comply with antenatal care.
» Manage pregnancy and postpartum period as there is a high-risk for adverse events.
» Select treatment options which are relatively safe in pregnancy.

MEDICINE TREATMENT

Treatment choice depends on course of illness; gender; comorbid medical conditions, substance use, or psychiatric conditions; and risk of non-adherence. Acute treatment should incorporate a long-term strategy. Combinations of medicines may be required, particularly in depression. (See algorithms below.)

Lithium is first-line option for long-term treatment:
» Response takes ± 1 week in mania and 6–8 weeks in depression.
» Prevents manic episodes by up to 40-50% and depressive episodes by up to 20-30% and reduces aggression, self-harm, and suicide.

- Lithium, oral, usual dose range 200–600 mg at night, depending on desired blood levels.
  - Pre-treatment: check eGFR, TFTs, calcium, and ECG in patients with cardiovascular risk factors. Proceed if eGFR and ECG are normal, and any thyroid or parathyroid disease is treated.
  - Initial dose: 400 mg (200 mg in elderly or high risk for renal disease).
  - Measure plasma trough concentration (at least 12 hours after previous dose):
    - First measurement: After 5 days of treatment.
    - Then 7 days after each dose change.
    - Then at 1 month and 3 months of treatment.
  - Document the number of hours since the last dose on the blood request form.
  - Lithium has a narrow therapeutic window. The therapeutic reference ranges are:
    - Acute mania: 0.8–1.0 mmol/L
    - Prevention of mania: 0.6–0.8 mmol/L
    - Prevention of depressive relapse: 0.4–0.8 mmol/L
  - Monitor lithium level and eGFR 6-monthly (3-monthly in elderly or medical comorbidity), and TSH and calcium annually.

CAUTION - LITHIUM

» Abrupt discontinuation may precipitate mania – taper slowly over 4 weeks.
» **Adverse effects** include nephrogenic diabetes insipidus, interstitial nephritis, chronic kidney disease; hypothyroidism; hyperparathyroidism; tremor.
» **Toxicity** occurs with levels >1.2 mmol/l (results in anorexia, nausea, diarrhoea, muscle weakness, drowsiness, ataxia, disorientation, seizures, coma, and death). Manage as for lithium poisoning (Section 19.9.2: Lithium poisoning).
» Risk of toxicity is increased with change to a low salt diet, dehydration, drug-drug interactions (diuretics, ACE-inhibitors, NSAIDs).
» Therapeutic drug monitoring is essential when using lithium.
» Clinical toxicity may even occur within the therapeutic range.

If patient has depressive symptoms and lamotrigine is poorly tolerated or not effective:

- Quetiapine, oral, usual dose range 100–300 mg at night (specialist prescribed).
  - Titrate to clinical effect, e.g.: Day 1: 50 mg. Day 2: 100 mg. Day 3: 200 mg. Day 4: 300 mg.
  - In the elderly and patients with hepatic impairment: Start with 25 mg and titrate up more slowly according to clinical effect.

LoE:IIIb[xxix]

PREGNANCY AND BREASTFEEDING

Valproate:

» Contraindicated in women of child-bearing potential due to high teratogenic risk (10%) and adverse neurodevelopmental outcomes (40%) with any pregnancy exposure. If no alternative, acknowledgment of risk must be signed: https://www.sahpra.org.za/wp-content/uploads/2025/05/GLF-CEM-PV-S01_v2-Valproate-Annual-Risk-Acknowledgement-Form-ARF.pdf

LoE:IIIb[xxx]

» If already on valproate: consult specialist and cross-titrate to an alternative medication if possible. Ensure folic acid supplementation. (See PHC STGs and EML, Section 16.6: Psychiatric patients – General monitoring and care.)

» Avoid valproate in breastfeeding as there is insufficient evidence to be sure of safety and it may be associated with adverse neurodevelopmental outcomes.

LoE:IIIb[xxxi]

Lithium:

» 1st trimester exposure is associated with increased risk of congenital anomalies.

» Refer for a fetal anomaly ultrasound at 18–22 weeks gestation.

» Adjust dose with physiological changes of pregnancy according to blood levels: monitor levels monthly, then weekly after 36 weeks and postpartum.

» Monitor fluid balance during and after delivery.

» Neonatal complications: goitre, nephrogenic diabetes insipidus, cardiac arrhythmias, cardiac failure, hypotonia, and lethargy.

» Excreted in breast milk, risk to the infant is unknown but toxicity may occur: breastfeeding is not recommended.

LoE:IIIb[xxxii]

Lamotrigine:

Increased hepatic clearance in pregnancy, but returns to normal post-partum; increase dose if necessary, according to clinical response and Figure 15.4 below.

May cause a rash in breastfed infant.

LoE:IIIb[xxxiii]

Antipsychotics:

» Considered safe, particularly quetiapine.

» They may increase the risk of gestational diabetes and obesity (especially olanzapine and clozapine).

» Clozapine: Do not stop in pregnancy due to risk of relapse of severe mental illness. Breastfeeding not recommended due to possible risk of agranulocytosis in the newborn.

Benzodiazepines: Avoid in pregnancy.

LoE:IVb[xxxiv]

Use only very short-term for severe distress.

LoE:IVb[xxxv]

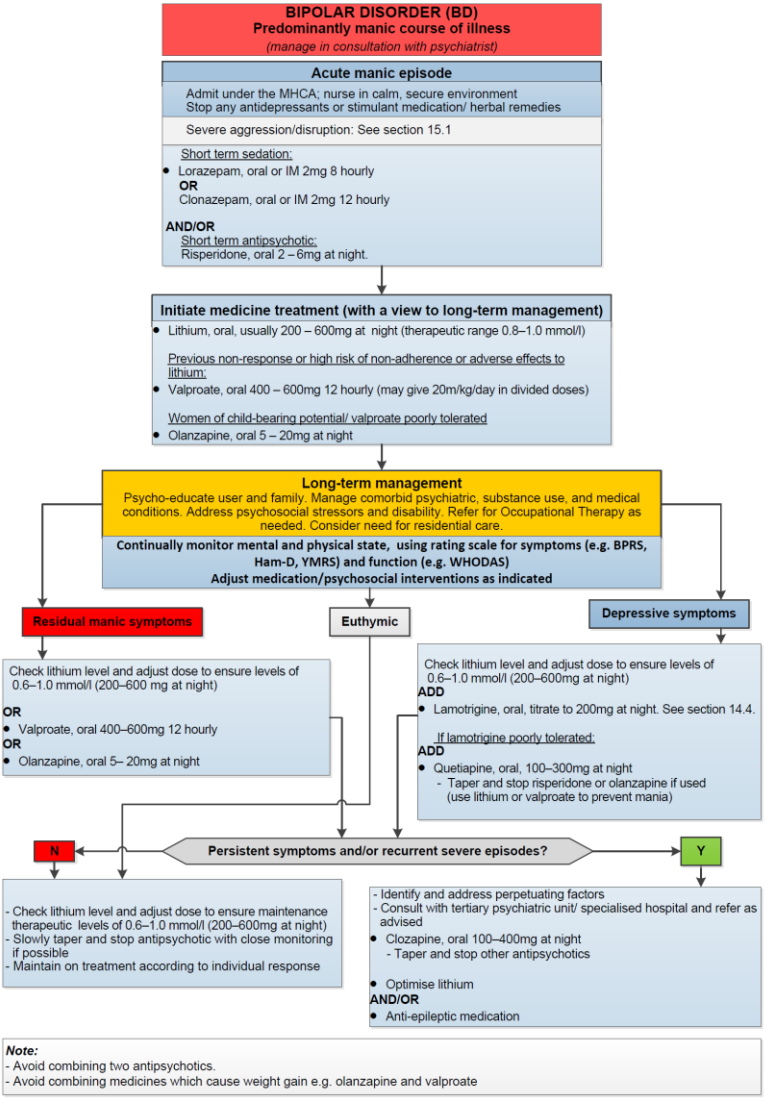


Figure 15.3: Algorithm for the management of bipolar disorder with predominantly manic course of illness *LoE:IIb*[xxxvi]

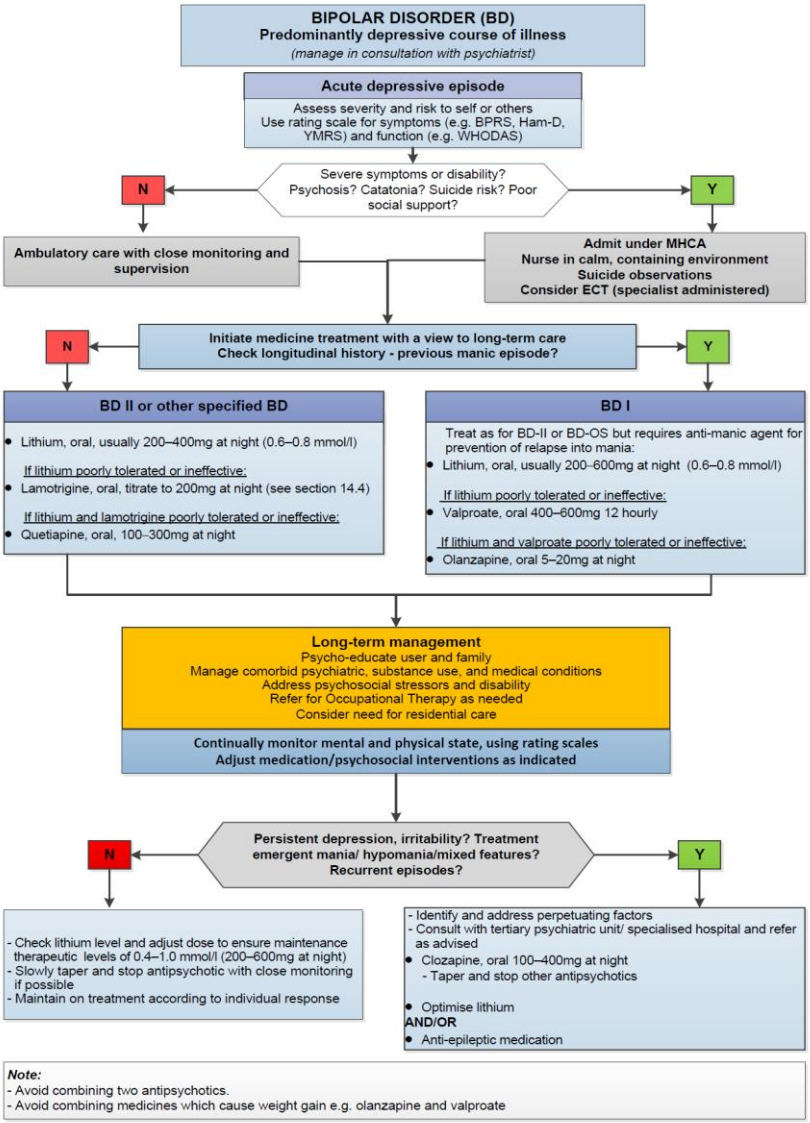


Figure 15.4: Algorithm for the management of bipolar disorder with predominantly depressive course of illness

LoE:IIb[xxxvii]

REFERRAL

All patients to be managed in consultation with a psychiatrist and to refer as advised, particularly if:

» High risk to self or others at any time.
» Rapid cycling (≥4 episodes despite treatment).
» Poor response to treatment with persistent depressive, manic, or mixed symptoms.

15.4 TRAUMA AND STRESS-RELATED DISORDERS

F43.0/F43.1/F43.2/F43.8-9 + (Z55-Z65)

DESCRIPTION

Acute stress and post-traumatic stress disorder arise in response to stressful events. The patient should have experienced the event as life threatening or as a physical threat to themselves or others, at which time they felt fear and helplessness.

A range of symptoms are associated with both of these conditions and include:

» re-experiencing of the event, e.g. flashbacks, dreams.
» avoidance of situations associated with the event.
» features of anxiety or increased arousal, e.g. hypervigilance, heightened startle response, and insomnia.

The conditions are symptomatically similar but differ with regard to the duration and time of onset of symptoms. The symptoms of acute stress disorder arise within 4 weeks of the event and last up to 4 weeks, whereas the symptoms of post-traumatic stress disorder last longer than 4 weeks and may arise more than 4 weeks after the traumatic incident.

GENERAL MEASURES

» Provide reassurance and support of patient and family.
» Assess risk to patient's safety: refer to police, social welfare and/or legal services as needed to ensure immediate safety.
» If patient has an ongoing/recent crisis: refer to social worker or registered counsellor for emotional containment and stress management.
» Psychotherapy, usually of a supportive / cognitive-behavioural nature.
» Trauma debriefing is not routinely recommended.

MEDICINE TREATMENT

Acute stress disorder:

Benzodiazepines may be useful in the immediate period following the traumatic event.

Prolonged use >1 week may be detrimental to adaptation, leading to higher rates of post-traumatic stress disorder.

For acute anxiety or agitation:

- Clonazepam, oral, 0.5–2 mg per day in 3 divided doses. *LoE:IVb*[xxxviii]

For sleep disturbance: See Section 15.6: Insomnia.

Post-traumatic stress-disorder:

- Selective serotonin reuptake inhibitors (SSRI), e.g.:
- Citalopram, oral, initial dose 20 mg daily. *LoE:IVb[xxxix]*

OR

- Fluoxetine, oral, initial dose 20 mg in the morning.

Note:

- A response to SSRI should be expected after 4–6 weeks.
- If there is no/partial response after 4–8 weeks, increase SSRI dose to 40 mg, if well tolerated.
- An adequate trial of treatment is 8–12 weeks, before an alternative treatment should be considered.
- Suicidal ideation may increase in the first few weeks of SSRI therapy. See PHC STGs and EML, 2023 – Section 16.7: Suicide risk assessment.

PREGNANCY AND BREASTFEEDING

» Perinatal PTSD is associated with low-birth-weight babies and poor mother-baby interactions.
» Experiences in pregnancy and childbirth may be traumatic and exacerbate existing PTSD or trigger new onset PTSD.
» Women with a history of childhood adversity, sexual abuse, or other previous trauma are at risk of perinatal PTSD.
» Treatment of PTSD in pregnancy is the same as for non-pregnant women.
» Avoid fluoxetine due to long half-life and relatively high concentration in breastmilk. Consider citalopram as alternative.
» All antidepressants: possible increased risk of miscarriage, transient neonatal symptoms (jitteriness, irritability), and persistent pulmonary hypertension of the newborn. Assess and discuss risk/benefit profile with patient.
» Avoid benzodiazepines – some association with neurodevelopmental delay in the child; neonatal sedation if used late in pregnancy.

LoE:IVb[xl]

REFERRAL

» Persistent symptoms.
» Inadequate response to treatment.
» Comorbid conditions.

15.5 PSYCHOTIC DISORDERS

DESCRIPTION

Psychosis is characterised by a loss of contact with reality. Psychotic disorders may present with:

» Delusions: Fixed beliefs which may manifest as disturbed speech content with persecutory, referential, grandiose, religiose, erotic, or bizarre themes.

» Hallucinations: Perceptual disturbances, e.g. auditory hallucinations, which are heard as voices distinct from the patients' thoughts.
» Disorganised thinking: Manifests as disordered flow of speech which impairs communication.
» Grossly disorganised or abnormal motor behaviour (including catatonia).
» Negative symptoms: reduced emotional expression, avolition, lack of speech, anhedonia, lack of social interaction.

Psychotic symptoms may occur in other psychiatric conditions (e.g. bipolar mania, major depression), medical conditions (e.g. certain types of epilepsy), or substance use (intoxication or withdrawal).

Psychosis is often accompanied by a lack of insight into the symptoms, poor judgement, and aggressive behaviour. The risk to self and others must always be assessed. It may be necessary to treat as an Assisted or Involuntary User under the MHCA.

15.5.1 ACUTE AND TRANSIENT PSYCHOTIC DISORDERS

F23.0-3/F23.8-9 + (F10.0-F19.9/R45.0-8/Z65.0-5/Z65.8-9/Z81.0-4/Z81.8)

DESCRIPTION

Sudden onset of ≥ 1 psychotic symptom (usually delusions, hallucinations, or disorganised thinking) which resolve spontaneously, usually within 1 month, with a full return to premorbid social or occupational functioning. Stressful events may precede the psychotic episode. Within 3 years, 40-50% will have a recurrent episode or develop schizophrenia or bipolar disorder.

LoE:IIb[xli]

GENERAL MEASURES

Assess and manage in consultation with a psychiatrist.

» Assess risk to self and others.
» Exclude and treat medical causes of psychotic symptoms (e.g. delirium, dementia, epilepsy).
» Exclude and manage substance use (e.g. cannabis, alcohol, amphetamines, and cocaine).
» Assess and treat other mental illness, e.g. anxiety disorders (see Section 15.2: anxiety and obsessive-compulsive disorders) and trauma and stress-related disorders. (See Section 15.4: Trauma and stress-related disorders.)
» Refer to social worker, psychologist or counselling services to address psycho-social stressors.
» Active follow-up is needed: commence treatment for schizophrenia or bipolar disorder if these become evident. (See Sections 15.3.2: Bipolar and related disorders and 15.5.2: Schizophrenia spectrum disorders.)

MEDICINE TREATMENT

» Manage severe aggressive or disruptive behaviour. (See Section 15.1: Aggressive disruptive behaviour in adults.)

» Treat according to underlying cause.

15.5.2 SCHIZOPHRENIA SPECTRUM DISORDERS

F20.0-6/F20.8-9/F22.0-9/F25.0-2/F25.8-9 + (F10.0-F19.9/R45.0-8/Z65.0-5/Z65.8-9/Z81.0-4/Z81.8)

DESCRIPTION

Schizophrenia is characterised by psychotic episodes which are severe, persistent, and accompanied by a marked deterioration in personal, social, and occupational functioning.

Whilst the presentation may be acute, the illness typically has a chronic, relapsing course with progressive cognitive and functional decline. Onset is usually in youth. Prognosis is worsened with delay in initial treatment, repeated episodes, and comorbid substance use. Comorbid metabolic syndrome and cardiovascular disease are common.

GENERAL MEASURES

» **Manage all patients in consultation with a psychiatrist.**
» Diagnostic certainty requires careful observation and re-evaluation over time.

Acute psychosis

» Assess risk to self and others.
» Clarify diagnosis.
» Manage within a multi-disciplinary team.
» Use shared decision-making in treatment process.
» Involve family and carers with patient's permission unless risk to self/others necessitates a breach of confidentiality.
» Provide psychoeducation to patient, family, and carers on the nature of the illness, need for continued treatment, how to self-monitor, early signs of relapse, and need for structure and routine.

Maintenance treatment

» Provide antipsychotic maintenance treatment to prevent relapse.
» Community-based nursing with adherence support, repeated risk assessment, and shared decision-making is required.
» Refer to occupational therapy for functional rehabilitation.
» Monitor psychiatric symptoms (use rating scales, e.g. BPRS or PANSS).
» Monitor extra-pyramidal side effects, weight, blood pressure, and glucose every 6 months.
» Adjust treatment according to response, adverse effects, and comorbidity.
» Provide lifestyle and dietary education; encourage exercise.
» Treat comorbid mood disorders (Section 15.3: Mood disorders).
» Treat comorbid hypertension (Section 3.6: Hypertension), diabetes mellitus (Section 8.5: Diabetes mellitus), and other medical conditions as needed.
» Manage substance use – refer for rehab (South African National Council on Alcoholism and Drug Dependence [SANCA], Social Development).

» Poor adherence with recurrent episodes:
  - Check reasons – illness, medication, patient factors.
  - Poor response/ tolerability to medication – change to alternative antipsychotic.
  - Poor insight - try depot antipsychotic – start with test dose (half initial dose in algorithm below).
  - Address psychosocial factors, substance use.
» Refer to social worker for placement in a residential home, day care or sheltered employment/workshop as needed.

Women of child-bearing potential: (See PHC STGs and EML, Section 6.9: Maternal mental health).
» Advise family planning – psycho-educate regarding need to plan pregnancy and comply with antenatal care.
» If patient is a parent/guardian – support childcare; refer to social worker if impaired.
» Risk of psychotic relapse is high in pregnancy and postpartum including the first year post-delivery.
» In pregnancy: continue antipsychotic treatment; Monitor closely for weight gain, gestational diabetes, psychotic relapse, and/or substance use.

MEDICINE TREATMENT

Acute psychotic episode

» Treat severe aggression and disturbed behaviour. (See Section 15.1: Aggressive disruptive behaviour in adults.)
» Initiate treatment with a view to long-term management.
» Assess risk factors for the development of tardive dyskinesia: age >50 years, female sex, prominent mood symptoms, cognitive or neurological disturbance e.g. intellectual disability, autistic spectrum, People living with HIV (PLHIV).
» In patients with high risk of tardive dyskinesia: Avoid haloperidol and antiparkinsonian medicines. Use chlorpromazine, risperidone or olanzapine at lowest doses needed to achieve desired effect. *LoE:IVb*[xlii]

Initiate treatment:

- Haloperidol, oral, 0.75–1.5 mg daily.
  - Increase to 5 mg daily if initial treatment tolerated and according to clinical response. *LoE:IVb*[xliii]

If good response/tolerability to haloperidol, or patient preference:

- Depot antipsychotic, e.g:
- Flupenthixol decanoate, IM, 10–40 mg every 4 weeks. *LoE:IVb*[xliv]
  - Initial dose: 10mg

OR

- Zuclopenthixol decanoate, IM, 100–400 mg every 4 weeks.
  - Initial dose: 100mg *LoE:III*[xlv]

If poor response / poorly tolerated / high risk of tardive dyskinesia / extra-pyramidal side effects:

- Risperidone, oral
  - Initial dose: 2–4 mg at night. *LoE:IIb[xlvi]*
  - Assess efficacy after 4–6 weeks:
    - If a partial response is noted, increase the dosage.
    - If no response is noted, switch treatment.
  - Maximum dose: 6 mg daily.

OR

- Chlorpromazine, oral, 75–300 mg at night, but may be increased to 800mg a day in 2–3 divided doses according to clinical response. *LoE:IVb[xlvii]*

If poor response/tolerability to haloperidol, risperidone, and chlorpromazine:

- Olanzapine, oral
  - Initial dose: 5 mg at night, increase to 10 mg at night.
  - Maximum dose: 20 mg at night. *LoE:IIb[xlviii]*

If poor response/tolerability to olanzapine:

- Clozapine, oral (specialist initiated, preferably as inpatient):
  - Initial dose: 12.5–25 mg at night.
  - Usual dose: 200–450 mg per day in 2 divided doses.
  - Maximum dose: 900 mg/day in 2 divided doses. *LoE:IVb[xlix]*

CAUTION - CLOZAPINE

» May cause neutropenia (3% of cases) and agranulocytosis (0.8% of cases):
- Pre-treatment: Check that white cell count and absolute neutrophil count are normal.
- Monitor absolute neutrophil count regularly.
- Withdraw clozapine and review medication if neutrophils <1.0 x109/L (general population).

» Myocarditis: highest risk in first two months of treatment. Monitor pulse, blood pressure, temperature; advise patient to report any palpitations, shortness of breath, chest pain, fever immediately.

» Seizures: risk increased at doses >450 mg/day.
- Manage as for epilepsy (Section 14.4: Epilepsy).
- Lamotrigine is preferred as it is weight neutral and does not interfere with clozapine metabolism.
- Avoid carbamazepine because of possible myelosuppression and enzyme induction.

» Constipation: avoid anticholinergics; may require laxatives; prolonged discomfort may indicate intestinal obstruction.

» Weight gain, diabetes, dyslipidaemia: Manage as per PHC STGs and EML, Section 16.6: Psychiatric patients general monitoring and care; Section 3.1: Ischaemic heart disease and atherosclerosis, prevention, and Section 8.5.1: Type 2 diabetes mellitus.

LoE:IVb[l]

OR

If poor response to olanzapine and clozapine is not an option due to metabolic effects (weight gain, type 2 diabetes) or persistent negative symptoms are present: LoE:IVb[ii]

» Refer to tertiary and quaternary level care for amisulpride if excessive weight gain and/or type 2 diabetes, or persistent negative symptoms. LoE:IVb[iii]

ADVERSE EFFECTS

Extrapyramidal adverse effects

Note: Anticholinergic medicines (e.g. orphenadrine) should not be added prophylactically to antipsychotics to prevent extrapyramidal side effects.

Acute dystonia: See the PHC STGs and EML, Section 16.2.1: Extra-pyramidal side effects.

Parkinsonism:

G21.0-1

- Anticholinergic agent, e.g.:
- Orphenadrine, oral, 50–150 mg daily according to individual response.
  - Usual dose: 50 mg 8 hourly.
  - Maximum dose: 150 mg daily.
  - Use with caution in the elderly as it may cause confusion and urinary retention.
  - Review antipsychotic treatment, and stop orphenadrine if medicine changed. LoE:IVb[iii]

Akathisia:

G25.8

A subjective unpleasant state of inner restlessness where there is a strong desire or compulsion to move:

- Propranolol, oral,
  - Start at 20 mg daily and titrate as needed up to 80 mg 8 hourly. LoE:IIIb[iv]
  - Monitor pulse and blood pressure.

Neuroleptic Malignant Syndrome:

See the PHC STGs and EML, Section 16.2.2: Neuroleptic malignant syndrome.

REFERRAL

All patients to be managed in consultation with a psychiatrist, refer as advised, particularly if:

» High risk to self or others at any time.
» If diagnosis is uncertain.
» Poor response to treatment.

15.6 INSOMNIA

G47.0/G47.9

DESCRIPTION

Insomnia may be an independent disorder or associated with comorbid conditions. Insomnia may persist despite successful treatment of the comorbidity and may necessitate separate treatment.

Patients presenting with insomnia may complain of difficulty falling asleep, frequent waking during the night, early-morning wakening, and daytime sleepiness.

GENERAL MEASURES

Treat the medical condition, psychiatric illness, substance use disorder or sleep disorder that may be precipitating or exacerbating the insomnia, if present.

Provide basic behavioural counselling about sleep hygiene and stimulus control as first step of treatment.

Cognitive behavioural therapy is the treatment of choice.

MEDICINE TREATMENT

If medication is needed:

Use the lowest effective dose.

Use intermittent dosing if possible (alternate night or less).

Sleep hygiene and stimulus control:

Maintain a regular sleep cycle (same time wake up in the morning, including week-ends).

Stimulus control:

- Keep the room quiet, dark, and at a comfortable temperature.
- Use the bed and bedroom only for sleeping and partner intimacy.

Limit intake of caffeine, nicotine, and alcohol, especially before bedtime.

Eat a light snack before bedtime and avoid eating large meals late at night.

Sleep restriction: avoid daytime naps.

Increase daily exercise (not late in the evening).

Practise anxiety management or relaxation techniques.

Go to bed only when tired. Sleep as much as needed to feel refreshed, not longer.

If unable to sleep despite attempting for more than 15–20 minutes, get out of bed and engage in a non-stimulating activity until tired (e.g. listen to soft music, read).

<u>If medication is needed to treat the insomnia:</u>

- Short-acting benzodiazepines, e.g.:
- Oxazepam, oral 7.5–30 mg at night.

Short-term use of benzodiazepines of 14 days is recommended, as long-term use is often associated with dependence.

LoE:IIb[lv]

REFERRAL

Patients with chronic insomnia.

15.7 DISCONTINUATION SYMPTOMS OF SEROTONIN REUPTAKE INHIBITORS

F19.3 + (Y49.2)

» Discontinuation symptoms are experienced due to receptor adaptation or receptor rebound after stopping of antidepressants. It can be avoided or reduced by slowly tapering the drug over at least 4 weeks.
» Symptoms include flu-like symptoms, 'shock-like" sensations, dizziness exacerbated by movement, insomnia, vivid dreaming and irritability, problems with concentration, and memory or movement disorders.
» It is managed by reintroduction of the SSRI and slower tapering of the dose.
» **Note:** Fluoxetine seldom causes discontinuation symptoms because of its long half-life.

15.8 SUBSTANCE USE DISORDERS

DESCRIPTION

Substance misuse is a general term which encompasses a range of substance use patterns including:

» Hazardous use – a risk of harmful consequences (social, mental, physical) to the user or others.
» Harmful use – the substance use causes harm to the user or others, and may be continuous or episodic (e.g. interpersonal violence after an alcohol binge).
» Dependence – characterised by a loss of self-regulation, repeated use despite harm, substance-induced mental illness, and withdrawal syndromes.

People with substance misuse present with related or comorbid health problems, e.g. to emergency rooms, infectious disease services (e.g. TB, HIV, Hepatitis, etc.); STD services; antenatal clinics; or mental health services.
Early identification and intervention of the substance use is advised to prevent further harm or dependence.

GENERAL MEASURES

» Screen for substance use disorders as a routine part of patient assessment, e.g. with WHO ASSIST[lvi]. The outcome of the screen should determine the level of intervention that is recommended– e.g. brief advice, a brief intervention (ASSIST linked brief intervention[lvii]) or referral to a local substance treatment programme (through a social worker or a registered NGO).
» Elective detoxification: plan in conjunction with a comprehensive substance treatment plan, co-ordinated by the Department of Social Development.
» Unplanned withdrawal: may occur during treatment for another medical condition or may be the presenting complaint. Provide brief intervention counselling and refer to a substance treatment programme.
» Injection drug use: counsel on harm reduction measures and refer to needle and syringe programmes, e.g. StepUp project[lviii] (TB HIV Care), OUT, Anova[lix] and COSUP[lx].

REFERRAL

» All patients treated for substance withdrawal should be referred to Social Services and/or a rehabilitation service for management of their substance use and aftercare.
» Discuss those with comorbid mental disorders with a psychiatrist; refer to specialist dual diagnosis services where available.
» Family and/or partners of people who use substances to registered counsellors and support groups (e.g., Al-anon family groups, https://www.alanon.org.za/).

15.8.1 ALCOHOL WITHDRAWAL

F10.3

GENERAL MEASURES

The following patients should be admitted for detoxification:

» past history of convulsions,
» past history of psychosis,
» suicidal ideation,
» significant medical comorbidity such as heart failure and liver disease,
» inadequate support at home,
» history of withdrawal delirium,
» >60 years of age,
» pregnancy,
» cognitive impairment,
» previous failed community detoxification attempts.

MEDICINE TREATMENT

Alcohol detoxification may be managed on an outpatient basis in most patients.

- Thiamine, oral, 300 mg daily for 14 days.

LoE:IIb[lxi]

AND

- Diazepam, oral, 10 mg immediately.
  - Then 5 mg 6 hourly for 3 days.
  - Then 5 mg 12 hourly for 2 days.
  - Then 5 mg daily for 2 days.
  - Then stop.

Note: Higher doses may be needed in individual patients.

15.8.1.1 ALCOHOL WITHDRAWAL DELIRIUM (DELIRIUM TREMENS)

F10.4

DESCRIPTION

Delirium typically occurs 2–3 days following cessation of prolonged alcohol intake, reaching a peak at around 5 days. However, some withdrawal symptoms, such as tremor, may start within 12 hours.

» Typical clinical features include:
  - visual hallucinations,
  - delusions,
  - disorientation, fluctuating level of consciousness,
  - agitation,
  - tonic-clonic seizures – these do not generally need long term anticonvulsant therapy,
  - tachycardia,
  - hypertension.
» It is important to consider alternative diagnoses, especially true in cases with an atypical presentation.
» Similar symptoms may occur following withdrawal from other sedative-hypnotic agents.
» Mortality varies from 1–5%.

GENERAL MEASURES

» For non-pharmacological management: See Section 20.8: Delirium.
» Cardiac monitoring and oximetry should be used when administering large doses of benzodiazepines.
» Assess for infections and other comorbid conditions.
» Ensure adequate hydration. Overhydration is a common error made in this setting.
» Correct abnormalities of electrolytes.
» Provide nutritional support.
» Consider referring appropriate patients to a rehabilitation programme after recovery from delirium tremens.

MEDICINE TREATMENT

Administer medicine doses according to severity of symptoms. These patients may require high doses of benzodiazepines because of hepatic enzyme induction.

- Benzodiazepines, e.g.:
- Diazepam, slow IV (max rate <5 mg/minute), 10 mg (**Not IM**).
  - Repeat dose after 5–10 minutes if required.
  - If this dose is not sufficient, use 10 mg every 5–10 minutes for another 1–3 doses to a maximum of 50 mg.

LoE:IVb[lxii]

Where intravenous access is not possible:

- Clonazepam, IM, 2 mg as a single dose.
  - If no response, repeat dose after 60 minutes until patient is sedated.
  - Repeat dose regularly to maintain mild sedation. *LoE:IVb*

OR

- Lorazepam, IM, 1–4 mg every 30–60 minutes until patient is sedated.
  - Repeat dose regularly to maintain mild sedation. *LoE: IVb*

Once patient is sedated, i.e. light somnolence, maintain mild sedation with:

- Diazepam, oral, 5–20 mg.
  - Repeat dose regularly to maintain mild sedation. *LoE: IVb*

CAUTION

Benzodiazepines, especially diazepam IV, can cause respiratory depression. Monitor patients closely as benzodiazepines can exacerbate an abnormal mental state or mask important neurological signs of deterioration.

Note:

» Lorazepam IM has slower onset of sedation than midazolam IM (32 vs 18 minutes) and longer duration of sedation (217 vs 82 minutes).

» Clonazepam oral or IM may be used if longer duration of sedation is required. Onset of action may be 30-60 minutes, time to maximum concentration is 1-4 hours. Long half-life (18-50 hours) increases risk of accumulation. Allow at least 12 hours between repeat doses. *LoE:IIb*[lxiii]

When administering glucose-containing fluids:

- Thiamine, oral/IM, 300 mg daily.

Note:

» Neuroleptic medicines such as haloperidol are associated with a reduced seizure threshold and QTc prolongation.

» **It is preferable to increase the dose of benzodiazepines than to add haloperidol.**

LoE:IVb[lxiv]

However, oral haloperidol may assist with managing hallucinations and agitation:

- Haloperidol, oral, 0.75–2.5 mg 12 hourly.
  - Maximum dose: 5mg per 24 hours.

LoE:IVb[lxv]

Do NOT use olanzapine, IM in the management of alcohol withdrawal. Olanzapine, IM may increase risk of respiratory depression if combined with parenteral benzodiazepines particularly if alcohol has been consumed.

15.8.2 OPIATE (E.G. HEROIN, UNGA, WHOONGA, NYAOPE) WITHDRAWAL

F11.2/F11.8-9

DESCRIPTION

Opioid withdrawal is generally poorly tolerated, but not dangerous, except in very frail debilitated patients or during pregnancy, with an increased risk of miscarriage in the first trimester and of preterm delivery in the third trimester.

Signs and symptoms of opioid intoxication:

- Pinpoint pupils
- Clammy skin
- Respiratory depression
- Drowsiness
- Euphoria
- Hallucinations

Signs and symptoms of opioid withdrawal:

- Nausea / vomiting
- Gooseflesh
- Abdominal cramps
- Rhinorrhoea and lacrimation
- Myalgia
- Diarrhoea
- Restlessness / agitation

GENERAL MEASURES:

» The identification and evidence-based management of opioid dependence among patients who are admitted to hospital will increase their likelihood of completing their primary admission-related treatment. Sub-optimal management of opioid withdrawal will increase the likelihood of absconding from hospital.

» It is extremely important to counsel patients managed for opioid withdrawal upon discharge. Patients' opioid tolerance will be reduced after the down-tapering of methadone (or similar medication) during hospital stay. Upon discharge, patients should be advised to use opioids with caution due to their increased risk of accidental overdose. Opioid related overdose deaths must be prevented.

» Special considerations apply during pregnancy, consult an expert.

» Concomitant withdrawal from opioids and other "downer" drugs, like benzodiazepines or alcohol may complicate withdrawal, consult an expert.

MEDICINE TREATMENT

Monitor for objective signs of withdrawal using a rating scale like the objective opioid withdrawal scale (OOWS):
https://medicine.yale.edu/sbirt/OOWS_251773_284_5_v1.pdf

LoE:IVb[lxvi]

Mild withdrawal (OOWS <4)
May be managed on an outpatient basis.

Symptomatic treatment

- Diazepam, oral, 5–20 mg/day in 2–3 divided doses.
  - Taper off over 5–7 days.

For stomach cramps:
- Hyoscine butylbromide, oral, 20 mg 8 hourly as required.

For headaches:
- Paracetamol, oral, 500 mg to 1 g, 4 to 6 hourly as required (to a maximum of 4 g in 24 hours).
  - Maximum dose: 15 mg/kg/dose. LoE:IVb[lxvii]

For muscle pains:
- NSAID, e.g.:
- Ibuprofen, oral 400 mg 8 hourly, with meals, as required.

LoE:IIb[lxviii]

For diarrhoea:
- Loperamide, oral, 4 mg immediately.
  - Then 2 mg after each loose stool.
  - Maximum dose: 16 mg in 24 hours.

Moderate to severe withdrawal (OOWS ≥4)
Hospitalise patient.

Opioid assisted withdrawal:
» Goal is to safely alleviate withdrawal symptoms without causing intoxication or overdose.
» Symptomatic medication listed above may be used to reduce methadone requirements.

Day 1:
Wait for early evidence of withdrawal (OOWS ≥4), then:
- Methadone, oral, 5–10 mg.
  - If symptoms are still present after 2–-4 hours, give another 5–10 mg.
  - Repeat until objective withdrawal symptoms are adequately managed (OOWS <4).
  - The total 24-hour dose should not be more than 30 mg. Consult a person experienced in opioid withdrawal if >30 mg/day is required.

Day 2:
- Methadone, oral.
  - Repeat total dose of day 1 as a single dose or 2 divided doses.
  - Monitor for ongoing signs and symptoms of withdrawal.
  - If the signs and symptoms of withdrawal are still present on day 2, top-up doses of 5 mg may be given at 2–4 hourly intervals with a total daily dose of up to 30 mg. Consult a person experienced in opioid withdrawal if symptoms are not controlled on 30 mg/day.

Day 3 onwards:
- Methadone, oral.
  - Repeat total dose from the previous day (e.g. day 2) if top-ups were needed, and begin dose reductions on the following day (e.g. day 4).

- If no top-ups required on the previous day (e.g. day 2) and withdrawal symptoms are adequately controlled, begin dose reduction.
- Decrease dose by 10–20% per day over a period of 3–10 days.
- The withdrawal regimen may be shortened if the patient's withdrawal symptoms allow.

LoE:IVb[lxix]

<u>If methadone is unavailable:</u>

- Tramadol, oral, 200 mg 12 hourly for 14 days may attenuate withdrawal symptoms.

LoE:IIIb[lxx]

Opioid poisoning

See Section: 19.5.3. Opioid poisoning.

REFERRAL

» Patients with an opioid use disorder should be offered a referral to access opioid substitution therapy and/or other evidence-based treatment and support.

» Patients identified with current/recent history of intravenous drug use should be provided with sterile injecting equipment (1 ml insulin needles and alcohol swabs) upon discharge from hospital, as well as referral to a community- based needle and syringe programme (See details in Section 15.8: Substance use disorders – General measures).

15.8.3 STIMULANT WITHDRAWAL, INCLUDING COCAINE AND AMPHETAMINE TYPE STIMULANTS (E.G. METHAMPHETAMINE/ TIK, METHCATHINONE/CAT)

F14.2/F15.2/F15.8-9

GENERAL MEASURES

These patients usually do not require admission.
Beware of depression and assess suicide risk.
Assess and monitor for psychosis.

MEDICINE TREATMENT

No substitute medication is available for detoxification.

<u>For severe anxiety, irritability, or withdrawal-related insomnia:</u>

- Benzodiazepines, short-term, e.g.:
- Diazepam, oral, 5–10 mg 8 hourly for 5–7 days.

15.8.4 METHAQUALONE (MANDRAX/WHITEPIPE) WITHDRAWAL

F19.2-4/F19.8-9

Withdrawal can be dangerous and may lead to seizures (see PHC STGs and EML, Section 21.2.11: Seizures and status epilepticus) or delirium (see Adult Hospital STGs and EML, Section 20.8: Delirium).

If withdrawal is symptomatic:

- Diazepam, oral, 5 mg 8 hourly.
  - Reduce over 3–5 days depending on clinical response.

15.8.5 CANNABIS WITHDRAWAL

F12.2

Withdrawal is rarely dangerous or poorly tolerated.
Assess for other accompanying psychiatric disorders e.g. mood or psychosis.

15.8.6 BENZODIAZEPINE WITHDRAWAL

F13.2

DESCRIPTION

Benzodiazepine addiction may occur after only a few weeks of use. Withdrawal symptoms may occur with abrupt dose reduction or cessation and include anxiety, nervousness, irritability, depersonalisation, delirium and seizures, increased sweating, sound sensitivity, nausea, difficulty concentrating, myoclonus, tremor, weakness, and fatigue.
Gradual tapering of the benzodiazepine is recommended to facilitate discontinuation.

GENERAL MEASURES

» The therapeutic relationship between client and doctor is extremely important in initiating dose reduction.
» Confirm benzodiazepine dependence – ascertain usage, history of previous withdrawal symptoms; a urine screen may be necessary.
» Establish full dosage of all benzodiazepines being taken, including those prescribed by other medical practitioners.
» Take time to explain negative impact of ongoing benzodiazepine use, benefits of stopping, and concepts like tolerance and withdrawal.
» Encourage the patient not to seek medication from other doctors.
» Evaluate and optimise management of comorbid substance use disorders, mental illness, and general health conditions.
» Avoid abrupt withdrawal of benzodiazepines; be prepared to take time. Negotiate each reduction with the patient. Individualise regular monitoring and motivation.
» Refer for substance use rehabilitation, e.g. SANCA (https://www.sancanational.info).

» Long-term follow-up with repeated motivation may be necessary to prevent relapse. *LoE:IIIb*[lxxi]

MEDICINE TREATMENT

» Replace short-acting benzodiazepine with an equivalent diazepam (long-acting benzodiazepine) dose.

» Patients may present with medicines that are unavailable in the public sector. *LoE:IVb*[lxxii]

Approximate equivalent doses to diazepam 5 mg are:

Alprazolam	0.25 mg
Bromazepam	1.5 mg
Clobazam	10 mg
Chlordiazepoxide	12.5 mg
Clonazepam	0.25 to 1 mg
Flunitrazepam	0.5 mg
Lorazepam	0.5 mg
Nitrazepam	5 mg
Oxazepam	15 mg
Temazepam	10 mg
Zolpidem	10 mg
Zopiclone	7.5 mg

Note:

» Medicines have only been included for comparison of estimated equivalent doses.

» Higher doses may be required for patients who are dependent on both alcohol and benzodiazepines. Inpatient assessment and initiation of benzodiazepine tapering may be warranted in these patients.

Reduction is done according to clinical response (see table below).

- Diazepam, oral.

Table 15.1: Dose reduction of diazepam-equivalent benzodiazepines

Daily diazepam-equivalent doses used	Dose reduction recommendation
> 50 mg/day	Reduce daily dose every 1–2 weeks by 10 mg/day until a daily dose of 50 mg is reached.
30-50 mg/day	Reduce every 1–2 weeks by 5 mg/day until a daily dose of 30 mg is reached.
20-29 mg/day	Reduce every 1–2 weeks by 2.5 mg/day until a daily dose of 20 mg is reached.
< 20 mg/day	Reduce every 1–2 weeks by 1.25 mg/day until stopped.

Note:

- If symptoms reappear, increase the dose by 2.5 or 5mg a day and then reduce dose using 2 to 4-week intervals.
- Do not prescribe more than one week's duration of medication at a time.

LoE:IIIb[lxxiii]

References:

[i] Definition (Psychoeducation): Sarkhel S, Singh OP, Arora M. Clinical Practice Guidelines for Psychoeducation in Psychiatric Disorders General Principles of Psychoeducation. Indian J Psychiatry. 2020 Jan;62(Suppl 2):S319-S323. doi: 10.4103/psychiatry.IndianJPsychiatry_780_19. Epub 2020 Jan 17. PMID: 32055073; PMCID: PMC7001357.

[ii] Definition (Manual Restraint): Strategies to end seclusion and restraint. WHO Quality Rights Specialized training. Course guide. Geneva: World Health Organization; 2019. Licence: CC BY-NC-SA 3.0 IGO. Available from: https://apps.who.int/iris/bitstream/handle/10665/329605/9789241516754-eng.pdf

[iii] Definition (Mechanical Restraint): National Department of Health. Policy Guidelines on Seclusion and Restraint of Mental Health Care Users. 2012. Available from: https://knowledgehub.health.gov.za/system/files/elibdownloads/2023-04/Policy%252520guidelines%252520on%252520seclusion%252520and%252520restraint%252520of%252520mental%252520health%252520care%252520users%2525202012.pdf

[iv] Management of aggressive disruptive behaviour in pregnancy: National Institute for Health and Clinical Excellence (NICE). Antenatal and postnatal mental health: the NICE guideline on clinical management and service guidance. Updated edition. NICE clinical guidance 192. London: NICE; 2014.

Management of aggressive disruptive behaviour in pregnancy: British Association for Psychopharmacology consensus guidance on the use of psychotropic medication preconception, in pregnancy and postpartum 2017. McAllister-Williams RH, Baldwin DS, Cantwell R, Easter A, Gilvarry E, Glover V, Green L, Gregoire A, Howard LM, Jones I, Khalifeh H, Lingford-Hughes A, McDonald E, Micali N, Pariante CM, Peters L, Roberts A, Smith NC, Taylor D, Wieck A, Yates LM, Young AH, endorsed by the British Association for Psychopharmacology. J Psychopharmacol. 2017;31:519. Available from: https://www.bap.uk

[v] Benzodiazepines: Zaman H, Sampson SJ, Beck AL, Sharma T, Clay FJ, Spyridi S, Zhao S, Gillies D. Benzodiazepines for psychosis-induced aggression or agitation. Cochrane Database Syst Rev. 2017 Dec 8;12:CD003079. https://www.ncbi.nlm.nih.gov/pubmed/29219171

[vi] Lorazepam, oral (dose range): Taylor, David; Paton, Carol; Kapur, Shitij. The Maudsley Prescribing Guidelines, Twelfth Edition. London: CRC Press; 2015.

Lorazepam, oral (dose range): South African Medicines Formulary. 14th Edition. Division of Clinical Pharmacology. University of Cape Town. 2022.

[vii] Clonazepam, oral (dose range): Taylor, David; Paton, Carol; Kapur, Shitij. The Maudsley Prescribing Guidelines, Twelfth Edition. London: CRC Press; 2015.

Clonazepam, oral (dose range): South African Medicines Formulary. 14th Edition. Division of Clinical Pharmacology. University of Cape Town. 2022.

[viii] Diazepam, oral (dose range): Taylor, David; Paton, Carol; Kapur, Shitij. The Maudsley Prescribing Guidelines, Twelfth Edition. London: CRC Press; 2015.

Diazepam, oral (dose range): South African Medicines Formulary. 14th Edition. Division of Clinical Pharmacology. University of Cape Town. 2022.

[ix] Midazolam, buccal: Taylor D, Okocha C, Paton C, Smith S, Connolly A. Buccal midazolam for agitation on psychiatric intensive care wards.Int J Psychiatry ClinPract.2008;12(4):309-11. http://www.ncbi.nlm.nih.gov/pubmed/24937720

Midazolam, buccal: National Department of Health, Essential Drugs Programme: Primary Health Care STGs and EML, 2018. http://www.health.gov.za/

Midazolam, oral: South African Medicines Formulary. 14th Edition. Division of Clinical Pharmacology. University of Cape Town. 2022.

[x] Olanzapine, oral: South African Medicines Formulary. 14th Edition. Division of Clinical Pharmacology. University of Cape Town. 2022.

Olanzapine, oral/oral dispersible tablet/IM/: National Department of Health: Affordable Medicines, EDP-Adult Hospital level. Medicine Review: Olanzapine for Aggressive / disruptive behaviour, 29 September 2022. https://www.knowledgehub.org.za/content/standard-treatment-guidelines-and-essential-medicines-list

[xi] Lorazepam, IM: Alexander J, Tharyan P, Adams C, John T, Mol C, Philip J. Rapid tranquillisation of violent or agitated patients in a psychiatric emergency setting. Pragmatic randomised trial of intramuscular lorazepam v. haloperidol plus promethazine. Br J Psychiatry. 2004 Jul;185:63-9. http://www.ncbi.nlm.nih.gov/pubmed/15231557

Lorazepam, IM (dose range): Taylor, David; Paton, Carol; Kapur, Shitij. The Maudsley Prescribing Guidelines, Tenth Edition. London: CRC Press; 2009.

[xii] Clonazepam, IM (dose range): Taylor, David; Paton, Carol; Kapur, Shitij. The Maudsley Prescribing Guidelines, Twelfth Edition. London: CRC Press; 2015.

[xiii] Benzodiazepine oral/IM repeat dosing: Nobay F, Simon BC, Levitt MA, Dresden GM. A prospective, double-blind, randomized trial of midazolam versus haloperidol versus lorazepam in the chemical restraint of violent and severely agitated patients. Acad Emerg Med. 2004 Jul;11(7):744-9. https://www.ncbi.nlm.nih.gov/pubmed/15231461

Benzodiazepine oral/IM repeat dosing: Patel MX, Sethi FN, Barnes TR, Dix R, Dratcu L, Fox B, Garriga M, Haste JC, Kahl KG, Lingford-Hughes A, McAllister-Williams H, O'Brien A, Parker C, Paterson B, Paton C, Posporelis S, Taylor DM, Vieta E, Völlm B, Wilson-Jones C, Woods L; With co-authors (in alphabetical order):. Joint BAP NAPICU evidence-based consensus guidelines for the clinical management of acute disturbance: De-escalation and rapid tranquillisation. J Psychopharmacol 2018 Jun;32(6):601-640. https://www.ncbi.nlm.nih.gov/pubmed/29882463

[xiv] Benzodiazepines, IM (onset of action/duration of action): Patel MX, Sethi FN, Barnes TR, Dix R, Dratcu L, Fox B, Garriga M, Haste JC, Kahl KG, Lingford-Hughes A, McAllister-Williams H, O'Brien A, Parker C, Paterson B, Paton C, Posporelis S, Taylor DM, Vieta E, Völlm B, Wilson-Jones C, Woods L; With co-authors (in alphabetical order):. Joint BAP NAPICU evidence-based consensus guidelines for the clinical management of acute disturbance: De-escalation and rapid tranquillisation. J Psychopharmacol. 2018 Jun;32(6):601-640. https://www.ncbi.nlm.nih.gov/pubmed/29882463

[xv] Benzodiazepines, parenteral: Gillies D, Sampson S, Beck A, Rathbone J. Benzodiazepines for psychosis-induced aggression or agitation. Cochrane Database Syst Rev. 2013 Apr 30;4:CD003079. http://www.ncbi.nlm.nih.gov/pubmed/23633309

[xvi] Zuclopenthixol acetate, IM: South African Medicines Formulary. 14th Edition. Division of Clinical Pharmacology. University of Cape Town. 2022.

[xvii] Thiamine, oral: Taylor DM, Barnes TRE, Young AH. The Maudsley Prescribing Guidelines in Psychiatry. 13th ed: WILEY Blackwell; 2018.

Thiamine: Lingford-Hughes AR, Welch S, Peters L, Nutt DJ; British Association for Psychopharmacology, Expert Reviewers Group. BAP updated guidelines: evidence-based guidelines for the pharmacological management of substance abuse, harmful use, addiction and comorbidity: recommendations from BAP. J Psychopharmacol. 2012 Jul;26(7):899-952. doi: 10.1177/0269881112444324. Epub 2012 May 23. PMID: 22628390.

[xviii] Fluoxetine, oral (anxiety): SSRIs (Therapeutic class): National Department of Health: Affordable Medicines, EDP- PHC and Adult Hospital level. Medicine Review: Selective serotonin reuptake inhibitors, therapeutic class for anxiety and depression, October 2017. http://www.health.gov.za/

Fluoxetine, oral (anxiety): Baldwin D, Woods R, Lawson R, Taylor D. Efficacy of drug treatments for generalised anxiety disorder: systematic review and meta-analysis. BMJ. 2011;342:d1199. https://www.ncbi.nlm.nih.gov/pubmed/21398351

Fluoxetine, oral (anxiety): Bandelow B, Reitt M, Rover C, Michaelis S, Gorlich Y, Wedekind D. Efficacy of treatments for anxiety disorders: a meta-analysis. Int Clin Psychopharmacol. 2015;30(4):183-92. https://www.ncbi.nlm.nih.gov/pubmed/25932596

Fluoxetine, oral (anxiety): Mayo-Wilson E, Dias S, Mavranezouli I, Kew K, Clark DM, Ades AE, et al. Psychological and pharmacological interventions for social anxiety disorder in adults: a systematic review and network meta-analysis. Lancet Psychiatry. 2014;1(5):368-76. https://www.ncbi.nlm.nih.gov/pubmed/26361000

Fluoxetine, oral (anxiety): South African Medicines Formulary. 14th Edition. Division of Clinical Pharmacology. University of Cape Town. 2022.

[xix] Citalopram, oral (anxiety): SSRIs (Therapeutic class): National Department of Health: Affordable Medicines, EDP- PHC and Adult Hospital level. Medicine Review: Selective serotonin reuptake inhibitors, therapeutic class for anxiety and depression, October 2017. http://www.health.gov.za/

Citalopram, oral (anxiety): Baldwin D, Woods R, Lawson R, Taylor D. Efficacy of drug treatments for generalised anxiety disorder: systematic review and meta-analysis. BMJ. 2011;342:d1199. https://www.ncbi.nlm.nih.gov/pubmed/21398351

Citalopram, oral (anxiety): Bandelow B, Reitt M, Rover C, Michaelis S, Gorlich Y, Wedekind D. Efficacy of treatments for anxiety disorders: a meta-analysis. Int Clin Psychopharmacol. 2015;30(4):183-92. https://www.ncbi.nlm.nih.gov/pubmed/25932596

Citalopram, oral (anxiety): Mayo-Wilson E, Dias S, Mavranezouli I, Kew K, Clark DM, Ades AE, et al. Psychological and pharmacological interventions for social anxiety disorder in adults: a systematic review and network meta-analysis. Lancet Psychiatry. 2014;1(5):368-76. https://www.ncbi.nlm.nih.gov/pubmed/26361000

Citalopram, oral (anxiety): Stahl SM, Gergel I, Li D. Escitalopram in the treatment of panic disorder: a randomized, double-blind, placebo-controlled trial. J Clin Psychiatry. 2003 Nov;64(11):1322-7. https://www.ncbi.nlm.nih.gov/pubmed/14658946

Citalopram, oral (anxiety): Thorlund K, Druyts E, Wu P, Balijepalli C, Keohane D, Mills E. Comparative efficacy and safety of selective serotonin reuptake inhibitors and serotonin-norepinephrine reuptake inhibitors in older adults: a network meta-analysis. J Am Geriatr Soc. 2015;63(5):1002-9. https://www.ncbi.nlm.nih.gov/pubmed/25945410

Citalopram, oral (anxiety): South African Medicines Formulary. 14th Edition. Division of Clinical Pharmacology. University of Cape Town. 2022.

[xx] Selective serotonin reuptake inhibitors, oral (resolution of agitation – anxiety disorders): South African Medicines Formulary. 14th Edition. Division of Clinical Pharmacology. University of Cape Town. 2022.

[xxi] Selective serotonin reuptake inhibitors, oral (duration of therapy – anxiety disorders): Rickels K, Etemad B, Khalid-Khan S, Lohoff FW, Rynn MA, Gallop RJ. Time to relapse after 6 and 12 months' treatment of generalized anxiety disorder with venlafaxine extended release. Arch Gen Psychiatry. 2010 Dec;67(12):1274-81. https://www.ncbi.nlm.nih.gov/pubmed/21135327

Selective serotonin reuptake inhibitors, oral (duration of therapy – anxiety disorders): World Health Organisation. mhGAP intervention guide for mental, neurological and substance use disorders in non-specialized health settings: mental health Gap Action Programme (mhGAP), version 2.0. Geneva, 2016 http://www.who.int/mental_health/mhgap/mhGAP_intervention_guide_02/en/

[xxii] Diazepam, oral (dosing in anxiety): British National Formulary, 78th edition (September 2019-March 2020).

Diazepam, oral (dosing in anxiety): South African Medicines Formulary. 14th Edition. Division of Clinical Pharmacology. University of Cape Town. 2022.

[xxiii] Benzodiazepines (caution): NICE. Generalised anxiety disorder and panicdisorder in adults: management, 26 January 2011. http://nice.org.uk/guidance/cg113

Benzodiazepines (caution): South African Medicines Formulary. 14th Edition. Division of Clinical Pharmacology. University of Cape Town. 2022.

Benzodiazepines, oral (caution): Picton JD, Marino AB, Nealy KL. Benzodiazepine use and cognitive decline in the elderly. Am J Health Syst Pharm. 2018 Jan 1;75(1):e6-e12. https://www.ncbi.nlm.nih.gov/pubmed/29273607

Benzodiazepines, oral (caution): Brandt J, Leong C. Benzodiazepines and Z-Drugs: An Updated Review of Major Adverse Outcomes Reported on in Epidemiologic Research. Drugs R D. 2017 Dec;17(4):493-507. https://www.ncbi.nlm.nih.gov/pubmed/28865038

[xxiv] Selective serotonin reuptake inhibitors, oral (in pregnancy): National Institute for Health and Clinical Excellence (NICE). Antenatal and postnatal mental health: the NICE guideline on clinical management and service guidance. Updated edition. NICE clinical guidance 192. London: NICE; 2014. Available from: https://www.nice.org.uk/guidance/cg192/evidence/full-guideline-pdf-19339686

Selective serotonin reuptake inhibitors, oral (in pregnancy): British Association for Psychopharmacology consensus guidance on the use of psychotropic medication preconception, in pregnancy and postpartum 2017. McAllister-Williams RH, Baldwin DS, Cantwell R, Easter A, Gilvarry E, Glover V, Green L, Gregoire A, Howard LM, Jones I, Khalifeh H, Lingford-Hughes A, McDonald E, Micali N, Pariante CM, Peters L, Roberts A, Smith NC, Taylor D, Wieck A, Yates LM, Young AH, endorsed by the British Association for Psychopharmacology. J Psychopharmacol. 2017;31:519. Available from: https://www.bap.uk

Sertraline, oral (perinatal anxiety and depression): National Department of Health: Affordable Medicines, EDP-Adult Hospital level. Medicine Review: Sertraline for Perinatal Anxiety and Depression, March 2020. http://www.health.gov.za/

[xxv] Selective serotonin reuptake inhibitors, oral (in pregnancy): National Institute for Health and Clinical Excellence (NICE). Antenatal and postnatal mental health: the NICE guideline on clinical management and service guidance. Updated edition. NICE clinical guidance 192. London: NICE; 2014. Available from: https://www.nice.org.uk/guidance/cg192/evidence/full-guideline-pdf-19339686

Selective serotonin reuptake inhibitors, oral (in pregnancy): British Association for Psychopharmacology consensus guidance on the use of psychotropic medication preconception, in pregnancy and postpartum 2017. McAllister-Williams RH, Baldwin DS, Cantwell R, Easter A, Gilvarry E, Glover V, Green L, Gregoire A, Howard LM, Jones I, Khalifeh H, Lingford-Hughes A, McDonald E, Micali N, Pariante CM, Peters L, Roberts A, Smith NC, Taylor D, Wieck A, Yates LM, Young AH, endorsed by the British Association for Psychopharmacology. J Psychopharmacol. 2017;31:519. Available from: https://www.bap.uk

Sertraline, oral (perinatal anxiety and depression): National Department of Health: Affordable Medicines, EDP-Adult Hospital level. Medicine Review: Sertraline for Perinatal Anxiety and Depression, March 2020. http://www.health.gov.za/

[xxvi] Selective serotonin reuptake inhibitors, oral (depression): SSRIs (Therapeutic class): National Department of Health: Affordable Medicines, EDP-PHC and Adult Hospital level. Medicine Review: SSRIs, therapeutic class for anxiety and depression, October 2017. http://www.health.gov.za/

Selective serotonin reuptake inhibitors, oral (depression): Cipriani A, Furukawa TA, Salanti G, Chaimani A, Atkinson LZ, Ogawa Y, Leucht S, Ruhe HG, Turner EH, Higgins JPT, Egger M, Takeshima N, Hayasaka Y, Imai H, Shinohara K, Tajika A, Ioannidis JPA, Geddes JR. Comparative efficacy and acceptability of 21 antidepressant drugs for the acute treatment of adults with major depressive disorder: a systematic review and network meta-analysis. Lancet. 2018 Apr 7;391(10128):1357-1366. https://www.ncbi.nlm.nih.gov/pubmed/29477251

Selective serotonin reuptake inhibitors , oral (depression): Magni LR, Purgato M, Gastaldon C, Papola D, Furukawa TA, Cipriani A, Barbui C. Fluoxetine versus other types of pharmacotherapy for depression. Cochrane Database Syst Rev. 2013 Jul 17;(7):CD004185. https://www.ncbi.nlm.nih.gov/pubmed/24353997

Selective serotonin reuptake inhibitors s, oral (depression): Thorlund K, Druyts E, Wu P, Balijepalli C, Keohane D, Mills E. Comparative efficacy and safety of selective serotonin reuptake inhibitors and serotonin-norepinephrine reuptake inhibitors in older adults: a network meta-analysis. J Am Geriatr Soc. 2015;63(5):1002-9. https://www.ncbi.nlm.nih.gov/pubmed/25945410

[xxvii] Amitryptiline, oral: South African Medicines Formulary. 14th Edition. Division of Clinical Pharmacology. University of Cape Town. 2022.

[xxviii] Selective serotonin reuptake inhibitors, oral (duration of therapy – depression): Bauer M, Severus E, Köhler S, Whybrow PC, Angst J, Möller HJ; Wfsbp
Task Force on Treatment Guidelines for Unipolar Depressive Disorders. World Federation of Societies of Biological Psychiatry (WFSBP) guidelines for biological treatment of unipolar depressive disorders. part 2: maintenance treatment of major depressive disorder-update 2015. World J Biol Psychiatry. 2015 Feb;16(2):76-95. https://www.ncbi.nlm.nih.gov/pubmed/25677972

Selective serotonin reuptake inhibitors, oral (duration of therapy – depression): World Health Organisation. mhGAP intervention guide for mental, neurological and substance use disorders in non-specialized health settings: mental health Gap Action Programme (mhGAP), version 2.0. Geneva, 2016
http://www.who.int/mental_health/mhgap/mhGAP_intervention_guide_02/en/

Selective serotonin reuptake inhibitors, oral (duration of therapy – depression): Geddes JR, Carney SM, Davies C, Furukawa TA, Kupfer DJ, Frank E, Goodwin GM. Relapse prevention with antidepressant drug treatment in depressive disorders: a systematic review. Lancet. 2003 Feb 22;361(9358):653-61. https://www.ncbi.nlm.nih.gov/pubmed/12606176

[xxix] Quetiapine, oral (acute treatment of depression and prevention of relapse): National Department of Health: Affordable Medicines, EDP-Adult Hospital level. Medicine Review: Quetiapine, oral for treatment and prevention of depression in bipolar disorder in adults, March 2019. http://www.health.gov.za/

Quetiapine, oral (depressive residual symptoms): Butler M, Urosevic S, Desai P, Sponheim SR, Popp J, Nelson VA, et al. Treatment for Bipolar Disorder in Adults: A Systematic Review. AHRQ Comparative Effectiveness Reviews. Rockville (MD) 2018. https://www.ncbi.nlm.nih.gov/books/NBK532183/

Quetiapine, oral (depressive residual symptoms): Miura T, Noma H, Furukawa TA, Mitsuyasu H, Tanaka S, Stockton S, et al. Comparative efficacy and tolerability of pharmacological treatments in the maintenance treatment of bipolar disorder: a systematic review and network meta-analysis. Lancet Psychiatry. 2014;1(5):351-9. https://www.ncbi.nlm.nih.gov/pubmed/26360999

Quetiapine, oral (depressive residual symptoms): Lindstrom L, Lindstrom E, Nilsson M, Hoistad M. Maintenance therapy with second generation antipsychotics for bipolar disorder - A systematic review and meta-analysis. Journal of affective disorders. 2017;213:138-50. https://www.ncbi.nlm.nih.gov/pubmed/28222360

Quetiapine, oral (depressive residual symptoms): Kessing LV, Bauer M, Nolen WA, Severus E, Goodwin GM, Geddes J. Effectiveness of maintenance therapy of lithium vs other mood stabilizers in monotherapy and in combinations: a systematic review of evidence from observational studies. Bipolar Disord. 2018 Feb 14.
https://www.ncbi.nlm.nih.gov/pubmed/29441712

Quetiapine, oral (dosing for treatment of depression in bipolar disorder): British National Formulary, 78th edition (September 2019-March 2020).

[xxx] Valproic acid – caution in pregnancy: European Medicines Agency - Pharmacovigilance Risk Assessment Committee. Assessment report EMA/198940/2018 - valproate exposure in pregnancy, 8 February 2018. http://www.ema.europa.eu/docs/en_GB/document_library/Referrals_document/Valproate_2017_31/Position_provided_by_CMDh/WC500250221.pdf
Valproic acid – caution in pregnancy: Meador K, Reynolds MW, Crean S, Fahrbach K, Probst C. Pregnancy outcomes in women with epilepsy: a systematic review and meta-analysis of published pregnancy registries and cohorts. Epilepsy Res. 2008 Sep;81(1):1-13. https://www.ncbi.nlm.nih.gov/pubmed/18565732
[xxxi] Valproate, oral (caution in pregnancy/breastfeeding): European Medicines Agency - Pharmacovigilance Risk Assessment Committee. Assessmentreport EMA/198940/2018 - valproate exposure in pregnancy, 8 February 2018. http://www.ema.europa.eu/docs/en_GB/document_library/Referrals_document/Valproate_2017_31/Position_provided_by_CMDh/WC500250221.pdf
Valproate (caution in pregnancy/breastfeeding): Veroniki AA, Rios P, Cogo E, Straus SE, Finkelstein Y, Kealey R, Reynen E, Soobiah C, Thavorn K, Hutton B, Hemmelgarn BR, Yazdi F, D'Souza J, MacDonald H, Tricco AC. Comparative safety of antiepileptic drugs for neurological development in children exposed during pregnancy and breast feeding: a systematic review and network meta-analysis. BMJ Open. 2017 Jul 20;7(7):e017248. doi: 10.1136/bmjopen-2017-017248. PMID: 28729328; PMCID: PMC5642793.
[xxxii] Lithium, oral (risk in pregnancy/breastfeeding): Munk-Olsen T, Liu X, Viktorin A, Brown HK, Di Florio A, D'Onofrio BM, Gomes T, Howard LM, Khalifeh H, Krohn H, Larsson H, Lichtenstein P, Taylor CL, Van Kamp I, Wesseloo R, Meltzer-Brody S, Vigod SN, Bergink V. Maternal and infant outcomes associated with lithium use in pregnancy: an international collaborative meta-analysis of six cohort studies. Lancet Psychiatry. 2018 Aug;5(8):644-652. https://www.ncbi.nlm.nih.gov/pubmed/29929874
[xxxiii] Lamotrigine, oral (risk in pregnancy/breastfeeding): South African Medicines Formulary. 14th Edition. Division of Clinical Pharmacology. University of Cape Town. 2022.
Lamotrigine, oral (risk in pregnancy/breastfeeding): Wesseloo R, Liu X, Clark CT, Kushner SA, Munk-Olsen T, Bergink V. Risk of postpartum episodes in women with bipolar disorder after lamotrigine or lithium use during pregnancy: A population-based cohort study. J Affect Disord. 2017 Aug 15;218:394-397. https://www.ncbi.nlm.nih.gov/pubmed/28501739
Lamotrigine, oral (risk in pregnancy/breastfeeding): Ding Y, Tan X, Zhang S, Guo Y. Pharmacokinetic changes and therapeutic drug monitoring of lamotrigine during pregnancy. Brain Behav. 2019 Jul;9(7):e01315. https://www.ncbi.nlm.nih.gov/pubmed/31104352
[xxxiv] Antipsychotics, oral (risk in pregnancy/breastfeeding): Uguz F. Antipsychotic Use During Pregnancy and the Risk of Gestational Diabetes Mellitus: A Systematic Review. J Clin Psychopharmacol. 2019 Mar/Apr;39(2):162-167. https://www.ncbi.nlm.nih.gov/pubmed/30624301
Antipsychotics, oral (risk in pregnancy/breastfeeding): Damkier P, Videbech P. The Safety of Second-Generation Antipsychotics During Pregnancy: A Clinically Focused Review. CNS Drugs. 2018 Apr;32(4):351-366. https://www.ncbi.nlm.nih.gov/pubmed/29637530
Antipsychotics, oral (risk in pregnancy/breastfeeding): Beex-Oosterhuis MM, Van Gool AR, Heerdink ER, van Kesteren C, van Marum RJ. Clozapine Treatment During Pregnancy and the Postpartum Period: A Systematic Literature Review. J Clin Psychiatry. 2021 Dec 14;83(1):21r13952. doi: 10.4088/JCP.21r13952. PMID: 34905664.
[xxxv] Benzodiazepines, oral (risk in pregnancy/breastfeeding): National Institute for Health and Clinical Excellence (NICE). Antenatal and postnatal mental health: the NICE guideline on clinical management and service guidance. Updated edition. NICE clinical guidance 192. London: NICE; 2014. Available from: https://www.nice.org.uk/guidance/cg192/evidence/full-guideline-pdf-19339686
[xxxvi] Bipolar disorder management (predominantly manic symptoms): National Department of Health: Affordable Medicines, EDP-Adult Hospital level. Medicine Review: Overview of management of bipolar disorders in adults, March 2019. http://www.health.gov.za/
Haloperidol, IM (aggressive/ disruptive behaviour in acute mania): Dundar Y, Greenhalgh J, Richardson M, Dwan K. Pharmacological treatment of acute agitation associated with psychotic and bipolar disorder: a systematic review and meta-analysis. Hum Psychopharmacol. 2016 Jul;31(4):268-85. https://www.ncbi.nlm.nih.gov/pubmed/27151529
Haloperidol, IM (aggressive/ disruptive behaviour in acute mania): Cipriani A, Rendell JM, Geddes JR. Haloperidol alone or in combination for acute mania. Cochrane Database Syst Rev. 2006 Jul 19;(3):CD004362. https://www.ncbi.nlm.nih.gov/pubmed/16856043
Risperidone, oral (acute treatment of mania): Butler M, Urosevic S, Desai P, Sponheim SR, Popp J, Nelson VA, et al. Treatment for Bipolar Disorder in Adults: A Systematic Review. AHRQ Comparative Effectiveness Reviews. Rockville (MD) 2018. https://www.ncbi.nlm.nih.gov/books/NBK532183/
Lithium, oral (acute manic symptoms): Butler M, Urosevic S, Desai P, Sponheim SR, Popp J, Nelson VA, et al. Treatment for Bipolar Disorder in Adults: A Systematic Review. AHRQ Comparative Effectiveness Reviews. Rockville (MD) 2018. https://www.ncbi.nlm.nih.gov/books/NBK532183/
Lithium, oral (prevention of manic relapse): National Department of Health: Affordable Medicines, EDP-Adult Hospital level. Medicine Review: Lithium, oral for acute and maintenance treatment of bipolar disorder in adults, October 2018. http://www.health.gov.za/
Valproate, oral (acute treatment of mania and prevention of relapse): Bipolar disorder management: National Department of Health: Affordable Medicines, EDP-Adult Hospital level. Medicine Review: Overview of management of bipolar disorders in adults, March 2019. http://www.health.gov.za/
Olanzapine, oral (acute treatment of mania and prevention of relapse): National Department of Health: Affordable Medicines, EDP-Adult Hospital level. Medicine Review: Olanzapine, oral for treatment and prevention of mania in bipolar disorder in adults, March 2019. http://www.health.gov.za/
Olanzapine, oral (acute treatment of mania): Butler M, Urosevic S, Desai P, Sponheim SR, Popp J, Nelson VA, et al.

Treatment for Bipolar Disorder in Adults: A Systematic Review. AHRQ Comparative Effectiveness Reviews. Rockville (MD)2018. https://www.ncbi.nlm.nih.gov/books/NBK532183/

Olanzapine, oral (prevention of manic relapse): Lindstrom L, Lindstrom E, Nilsson M, Hoistad M. Maintenance therapy with second generation antipsychotics for bipolar disorder - A systematic review and meta-analysis. Journal of affective disorders. 2017;213:138-50. https://www.ncbi.nlm.nih.gov/pubmed/28222360

Olanzapine, oral (prevention of manic relapse): Miura T, Noma H, Furukawa TA, Mitsuyasu H, Tanaka S, Stockton S, et al. Comparative efficacy and tolerability of pharmacological treatments in the maintenance treatment of bipolar disorder: a systematic review and network meta-analysis. Lancet Psychiatry. 2014;1(5):351-9. https://www.ncbi.nlm.nih.gov/pubmed/26360999

Clozapine, oral (refractory bipolar disorder). National Department of Health: Affordable Medicines, EDP-Adult Hospital level. Medicine Review: Clozapine for refractory bipolar disorders in adults, March 2019. http://www.health.gov.za/

Clozapine, oral (refractory bipolar disorder): Li XB, Tang YL, Wang CY, de Leon J. Clozapine for treatment-resistant bipolar disorder: a systematic review. Bipolar Disord. 2015 May;17(3):235-47. https://www.ncbi.nlm.nih.gov/pubmed/25346322

[xxxvii] Bipolar disorder management (predominantly depressive symptoms): National Department of Health: Affordable Medicines, EDP-Adult Hospital level. Medicine Review: Overview of management of bipolar disorders in adults, March 2019. http://www.health.gov.za/

Lithium, oral (depressive residual symptoms): National Department of Health: Affordable Medicines, EDP-Adult Hospital level. Medicine Review: Lithium, oral for bipolar disorders in adults, October 2018. http://www.health.gov.za/

Lamotrigine, oral (depressive residual symptoms and prevention of depressive relapse): Bipolar disorder management: National Department of Health: Affordable Medicines, EDP-Adult Hospital level. Medicine Review: Overview of management of bipolar disorders in adults, March 2019. http://www.health.gov.za/

Lamotrigine, oral (depressive residual symptoms and prevention of depressive relapse): Miura T, Noma H, Furukawa TA, Mitsuyasu H, Tanaka S, Stockton S, et al. Comparative efficacy and tolerability of pharmacological treatments in the maintenance treatment of bipolar disorder: a systematic review and network meta-analysis. Lancet Psychiatry. 2014;1(5):351-9. https://www.ncbi.nlm.nih.gov/pubmed/26360999

Quetiapine, oral (acute treatment of depression and prevention of relapse): National Department of Health: Affordable Medicines, EDP-Adult Hospital level. Medicine Review: Quetiapine, oral for treatment and prevention of depression in bipolar disorder in adults, March 2019. http://www.health.gov.za/

Quetiapine, oral (depressive residual symptoms): Butler M, Urosevic S, Desai P, Sponheim SR, Popp J, Nelson VA, et al. Treatment for Bipolar Disorder in Adults: A Systematic Review. AHRQ Comparative Effectiveness Reviews. Rockville (MD) 2018. https://www.ncbi.nlm.nih.gov/books/NBK532183/

Quetiapine, oral (depressive residual symptoms): Miura T, Noma H, Furukawa TA, Mitsuyasu H, Tanaka S, Stockton S, et al. Comparative efficacy and tolerability of pharmacological treatments in the maintenance treatment of bipolar disorder: a systematic review and network meta-analysis. Lancet Psychiatry. 2014;1(5):351-9. https://www.ncbi.nlm.nih.gov/pubmed/26360999

Quetiapine, oral (depressive residual symptoms): Lindstrom L, Lindstrom E, Nilsson M, Hoistad M. Maintenance therapy with second generation antipsychotics for bipolar disorder - A systematic review and meta-analysis. Journal of affective disorders. 2017;213:138-50. https://www.ncbi.nlm.nih.gov/pubmed/28222360

Quetiapine, oral (depressive residual symptoms): Kessing LV, Bauer M, Nolen WA, Severus E, Goodwin GM, Geddes J. Effectiveness of maintenance therapy of lithium vs other mood stabilizers in monotherapy and in combinations: a systematic review of evidence from observational studies. Bipolar Disord. 2018 Feb 14. https://www.ncbi.nlm.nih.gov/pubmed/29441712

Clozapine, oral (refractory bipolar disorder). National Department of Health: Affordable Medicines, EDP-Adult Hospital level. Medicine Review: Clozapine for refractory bipolar disorders in adults, March 2019. http://www.health.gov.za/

Clozapine, oral (refractory bipolar disorder): Li XB, Tang YL, Wang CY, de Leon J. Clozapine for treatment-resistant bipolar disorder: a systematic review. Bipolar Disord. 2015 May;17(3):235-47. https://www.ncbi.nlm.nih.gov/pubmed/25346322

[xxxviii] Clonazepam – acute stress disorder: Mellman TA, Byers PM, Augenstein JS. Pilot evaluation of hypnotic medication during acute traumatic stress response. J Trauma Stress. 1998 Jul;11(3):563-9.

Clonazepam – acute stress disorder: Tol WA, Barbui C, van Ommeren M. Management of acute stress, PTSD, and bereavement: WHO recommendations. JAMA. 2013 Aug 7;310(5):477-8.

[xxxix] Selective serotonin reuptake inhibitors – post-traumatic stress disorder: Mellman TA, Byers PM, Augenstein JS. Pilot evaluation of hypnotic medication during acute traumatic stress response. J Trauma Stress. 1998 Jul;11(3):563-9. https://www.ncbi.nlm.nih.gov/pubmed/9690193

Selective serotonin reuptake inhibitors – post-traumatic stress disorder: Tol WA, Barbui C, van Ommeren M. Management of acute stress, PTSD, and bereavement: WHO recommendations. JAMA. 2013 Aug 7;310(5):477-8. https://www.ncbi.nlm.nih.gov/pubmed/23925613

[xl] Pregnancy and breast feeding: Cook N, Ayers S, Horsch A. Maternal posttraumatic stress disorder during the perinatal period and child outcomes: A systematic review. J Affect Disord. 2018 Jan 1;225:18-31. doi:10.1016/j.jad.2017.07.045. Epub 2017 Jul 27. PMID: 28777972.

Pregnancy and breast feeding: Laifer LM, O'Hara MW, DiLillo D, Brock RL. Risk for trauma-related distress following difficult childbirth: Trajectories of traumatic intrusions across 2 years postpartum. Arch Womens Ment Health. 2023 Apr;26(2):191-200. doi: 10.1007/s00737-023-01296-2. Epub 2023 Jan 31. PMID: 36719513; PMCID: PMC10083078.

Pregnancy and breast feeding: Dozio E, Feldman M, Bizouerne C, Drain E, Laroche Joubert M, Mansouri M, Moro MR, Ouss L. The Transgenerational Transmission of Trauma: The Effects of Maternal PTSD in Mother-Infant Interactions. Front Psychiatry. 2020 Nov 30;11:480690. doi: 10.3389/fpsyt.2020.480690. PMID: 33329072; PMCID: PMC7733963.

Pregnancy and breast feeding: Cirino NH, Knapp JM. Perinatal Posttraumatic Stress Disorder: A Review of Risk Factors, Diagnosis, and Treatment. Obstet Gynecol Surv. 2019 Jun;74(6):369-376. doi: 10.1097/OGX.0000000000000680. PMID: 31216046.

[xlii] Acute psychosis (prognosis): Fusar-Poli P, Cappucciati M, Bonoldi I, Hui LM, Rutigliano G, Stahl DR, Borgwardt S, Politi P, Mishara AL, Lawrie SM, Carpenter WT Jr, McGuire PK. Prognosis of Brief Psychotic Episodes: A Meta-analysis. JAMA Psychiatry. 2016 Mar;73(3):211-20. https://www.ncbi.nlm.nih.gov/pubmed/26764163

[xliii] Tardive dyskinesia (high risk factors): Correll CU, Kane JM, Citrome LL. Epidemiology, Prevention, and Assessment of Tardive Dyskinesia and Advances in Treatment. J Clin Psychiatry. 2017 Sep/Oct;78(8):1136-1147. https://www.ncbi.nlm.nih.gov/pubmed/29022654

[xliii] Haloperidol, oral: South African Medicines Formulary. 14th Edition. Division of Clinical Pharmacology. University of Cape Town. 2022.

[xliv] Flupenthixol decanoate, IM: South African Medicines Formulary. 14th Edition. Division of Clinical Pharmacology. University of Cape Town. 2022.

[xlv] Zuclopenthixol decanoate, IM: South African Medicines Formulary. 14th Edition. Division of Clinical Pharmacology. University of Cape Town. 2022.

[xlvi] Risperidone, oral: Leucht S, Corves C, Arbter D, Engel RR, Li C, Davis JM. Second-generation versus first-generation antipsychotic drugs for schizophrenia: a meta-analysis. Lancet. 2009 Jan 3;373(9657):31-41. http://www.ncbi.nlm.nih.gov/pubmed/19058842

Risperidone, oral: Crespo-Facorro B, Pérez-Iglesias R, Mata I, Ramirez-Bonilla M, Martínez-Garcia O, Pardo-Garcia G, Caseiro O, Pelayo-Terán JM, Vázquez-Barquero JL. Effectiveness of haloperidol, risperidone and olanzapine in the treatment of first-episode non-affective psychosis: results of a randomized, flexible-dose, open-label 1-year follow-up comparison. J Psychopharmacol.2011 Jun;25(6):744-54. http://www.ncbi.nlm.nih.gov/pubmed/21292922

[xlvii] Chlorpromazine, oral: South African Medicines Formulary. 14th Edition. Division of Clinical Pharmacology. University of Cape Town. 2012.

[xlviii] Olanzapine, oral: Leucht S, Cipriani A, Spineli L, Mavridis D, Orey D, Richter F, Samara M, Barbui C, Engel RR, Geddes JR, Kissling W, Stapf MP, Lässig B, Salanti G, Davis JM. Comparative efficacy and tolerability of 15 antipsychotic drugs in schizophrenia: a multiple-treatments meta-analysis. Lancet. 2013 Sep 14;382(9896):951-62. https://www.ncbi.nlm.nih.gov/pubmed/23810019

Olanzapine, oral: Krause M, Zhu Y, Huhn M, Schneider-Thoma J, Bighelli I, Nikolakopoulou A, Leucht S. Antipsychotic drugs for patients with schizophrenia and predominant or prominent negative symptoms: a systematic review and meta-analysis. Eur Arch Psychiatry Clin Neurosci. 2018 Oct;268(7):625-639. https://www.ncbi.nlm.nih.gov/pubmed/29368205

Olanzapine, oral: National Department of Health: Affordable Medicines, EDP-Adult Hospital level. Medicine Review: Olanzapine, oral for schizophrenia and related disorders, June 2019. http://www.health.gov.za/

[xlix] Orphenadrine, oral: South African Medicines Formulary. 14th Edition. Division of Clinical Pharmacology. University of Cape Town. 2022.

[l] Clozapine, oral (caution): FDA Drug Safety Communication: FDA modifies monitoring for neutropenia associated with schizophrenia medicine clozapine, 2015. https://www.fda.gov/drugs/drug-safety-and-availability/fda-drug-safety-communication-fda-modifies-monitoring-neutropenia-associated-schizophrenia-medicine

Clozapine, oral (caution): Taylor, David; Paton, Carol; Kapur, Shitij. The Maudsley Prescribing Guidelines, Twelfth Edition. London: CRC Press; 2015.

Clozapine, oral (caution): South African Medicines Formulary. 14th Edition. Division of Clinical Pharmacology. University of Cape Town. 20226.

[li] Clozapine, oral: South African Medicines Formulary. 14th Edition. Division of Clinical Pharmacology. University of Cape Town. 2022.

[lii] Amisulpiride, oral: National Department of Health, Essential Drugs Programme: Tertiary and Quaternary EML, 2019. http://www.health.gov.za/

[liii] Amisulpiride, oral: National Department of Health, Essential Drugs Programme: Tertiary and Quaternary EML, 2019. http://www.health.gov.za/

[liv] Propanolol, oral: Poyurovsky M, Pashinian A, Weizman R, Fuchs C, Weizman A. Low-dose mirtazapine: a new option in the treatment of antipsychotic-induced akathisia. A randomized, double-blind, placebo- and propranolol-controlled trial. Biol Psychiatry 2006; 59: 1071– 7.http://www.ncbi.nlm.nih.gov/pubmed /16497273

[lv] Oxazepam:Buscemi N, Vandermeer B, Friesen C, Bialy L, Tubman M, Ospina M, Klassen TP, Witmans M. The efficacy and safety of drug treatments for chronic insomnia in adults: a meta-analysis of RCTs. J Gen Intern Med. 2007 Sep;22(9):1335-50. http://www.ncbi.nlm.nih.gov/pubmed/17619935

Oxazepam, oral: South African Medicines Formulary. 14th Edition. Division of Clinical Pharmacology. University of Cape Town. 2022.

[lvi] Tool for screening for substance use disorders WHO Assist tool. https://www.who.int/publications/i/item/978924159938-2

[lvii] Tool for brief intervention for substance use disorders: ASSIST https://apps.who.int/iris/bitstream/handle/10665/44321/9789241599399_eng.pdf;jsessionid=BE4E60013BFEDCFFBDFF4B1DE1DE097A?sequence=1

[lviii] Needle and syringe programme: https://tbhivcare.org/

[lix] Needle and syringe programme: https://www.anovahealth.co.za/clinical-interest-areas/prevention/harm-reduction/

[lx] Needle and syringe programme: https://www.facebook.com/pages/COSUP-Community-Oriented-Substance-Use-Programme/480035362389140

[lxi] Thiamine, oral: Day E, Bentham PW, Callaghan R, Kuruvilla T, George S. Thiamine for prevention and treatment of Wernicke-Korsakoff Syndrome in people who abuse alcohol. Cochrane Database Syst Rev. 2013 Jul 1;7:CD004033. http://www.ncbi.nlm.nih.gov/pubmed/23818100

Thiamine: Lingford-Hughes AR, Welch S, Peters L, Nutt DJ; British Association for Psychopharmacology, Expert Reviewers Group. BAP updated guidelines: evidence-based guidelines for the pharmacological management of substance abuse, harmful use, addiction and comorbidity: recommendations from BAP. J Psychopharmacol. 2012 Jul;26(7):899- 952. http://www.ncbi.nlm.nih.gov/pubmed/22628390

lxii Diazepam, oral: South African Medicines Formulary, 14th Edition. Division of Clinical Pharmacology. University of Cape Town, 2022.

[lxiii] Benzodiazepines, parenteral: Gillies D, Sampson S, Beck A, Rathbone J. Benzodiazepines for psychosis-induced aggression or agitation. Cochrane Database Syst Rev. 2013 Apr 30;4:CD003079. http://www.ncbi.nlm.nih.gov/pubmed/23633309

[lxiv] Benzodiazepines: National Institute for Health and Clinical Excellence (NICE). Alcohol-use disorders: diagnosis, assessment and management of harmful drinking (high-risk drinking) and alcohol dependence. NICE clinical guidance 115. London: NICE; 2011. Available from: https://www.nice.org.uk/guidance/cg115.

[lxv] Haloperidol: Taylor, David; Paton, Carol; Kapur, Shitij. The Maudsley Prescribing Guidelines, Twelfth Edition. London: CRC Press; 2015..

[lxvi] Objective opioid withdrawal scale (OOWS) rating scale: Handelsman L, Cochrane KJ, Aronson MJ, Ness R, Rubinstein KJ, Kanof PD. Two new rating scales for opiate withdrawal. Am J Drug Alcohol Abuse. 1987;13(3):293-308. https://www.ncbi.nlm.nih.gov/pubmed/3687892

[lxvii] Paracetamol, oral: South African Medicines Formulary, 14th Edition. Division of Clinical Pharmacology. University of Cape Town, 2022.

[lxviii] NSAIDs as a therapeutic class (diclofenac, naproxen, ibuprofen): Affordable Medicines, EDP-Adult Hospital level. NSAIDs – comparative review of efficacy and safety, 15 January2018. http://www.health.gov.za

NSAIDs as a therapeutic class (diclofenac, naproxen, ibuprofen): Van Walsem A, Pandhi S, Nixon RM, Guyot P, Karabis A, Moore RA. Relative benefit-risk comparing diclofenac to other traditional non-steroidal anti-inflammatory drugs and cyclooxygenase-2 inhibitors in patients with osteoarthritis or rheumatoid arthritis: a network meta-analysis. Arthritis Research & Therapy 2015;17:66. https://www.ncbi.nlm.nih.gov/pubmed/25879879

NSAIDs as a therapeutic class (diclofenac, naproxen, ibuprofen): Nissen SE, Yeomans ND, Solomon DH, Lüscher TF, et al. Cardiovascular Safety of Celecoxib, Naproxen, or Ibuprofen for Arthritis. N Engl J Med 2016;375:2519-29. https://www.ncbi.nlm.nih.gov/pubmed/28379793

NSAIDs as a therapeutic class (diclofenac, naproxen, ibuprofen): Coxib and traditional NSAID Trialists' (CNT) Collaboration. Vascular and upper gastrointestinal effects of non-steroidal anti-inflammatory drugs: meta-analyses of individual participant data from randomised trials. Lancet 2013; 382: 769–79. https://www.ncbi.nlm.nih.gov/pubmed/23726390

NSAIDs as a therapeutic class (diclofenac, naproxen, ibuprofen): Trelle S, Reichenbach S, Wandel S, Hildebrand P, Tschannen B, et al. Cardiovascular safety of non-steroidal anti-inflammatory drugs: network meta-analysis. BMJ 2011;342:c7086. https://www.ncbi.nlm.nih.gov/pubmed/21224324

NSAIDs as a therapeutic class (diclofenac, naproxen, ibuprofen): Ong CKS, Lirk P, Tan Ch, Seymour RA. An evidence-based update on nonsteroidal anti-inflammatory drugs. Clinical Medicine and Research 2007; 5(1):19-34. https://www.ncbi.nlm.nih.gov/pubmed/17456832

NSAIDs as a therapeutic class (diclofenac, naproxen, ibuprofen): Stam WB, Jansen JP, Taylor SD. Efficacy of etoricoxib, lumiracoxib, non-selective NSAIDs, and acetaminophen in osteoarthritis: a mixed treatment comparison. The Open Rheumatology Journal 2012; 6:6-20. https://www.ncbi.nlm.nih.gov/pubmed/22582102

NSAIDs as a therapeutic class (diclofenac, naproxen, ibuprofen): Bello AE, Holt RJ. Cardiovascular risk with non-steroidal anti-inflammatory drugs: clinical implications. Drug Saf. 2014 Nov;37(11):897-902. https://www.ncbi.nlm.nih.gov/pubmed/25079141

NSAIDs as a therapeutic class (diclofenac, naproxen, ibuprofen): South African Medicines Formulary, 14th Edition. Division of Clinical Pharmacology. University of Cape Town, 2022.

[lxix] Methadone, oral: National Department of Health. National Policy guidelines on detoxification of psychoactive substances. http://www.health.gov.za/

Methadone, oral: Weich L, Nowbath H, Flegar S, Mahomedy Z, Ramjee H, Hitzeroth V, et al. South African guidelines for the management of opioid dependence. Updated 2013. Pretoria: South African Addiction Medicine Society; 2013. https://www.saams.co.za/Content/Documents/South_African_Guidelines_for_the_Management_of_Opioid_use_disorders_2015.pdf

[lxx] Tramadol, oral: Chattopadhyay S, Singh OP, Bhattacharyya A, Sen S, Roy P, Debnath S. Tramadol versus clonidine in management of heroin withdrawl. Asian J Psychiatr. 2010 Dec;3(4):237-9. http://www.ncbi.nlm.nih.gov/pubmed/23050896

Tramadol, oral: Lofwall MR, Babalonis S, Nuzzo PA, Siegel A, Campbell C, Walsh SL. Efficacy of extended-release tramadol for treatment of prescription opioid withdrawal: a two-phase randomized controlled trial. Drug Alcohol Depend. 2013 Nov 1;133(1):188-97. http://www.ncbi.nlm.nih.gov/pubmed/23755929

Tramadol, oral: Lofwall MR, Walsh SL, Bigelow GE, Strain EC. Modest opioid withdrawal suppression efficacy of oral tramadol in humans. Psychopharmacology (Berl). 2007 Oct;194(3):381-93. http://www.ncbi.nlm.nih.gov/pubmed/17605004

[lxxi] Benzodiazepine detoxification (non-pharmacological measures): Darker CD, Sweeney BP, Barry JM, Farrell MF, Donnelly-Swift E. Psychosocial interventions for benzodiazepine harmful use, abuse or dependence. Cochrane Database Syst Rev. 2015;(5):CD009652. https://www.ncbi.nlm.nih.gov/pubmed/26106751

[lxxii] Approximate equivalent doses of diazepam, oral 5mg: British National Formulary, 78th edition (September 2019-March 2020).

Approximate equivalent doses of diazepam, oral 5mg: Taylor, David; Paton, Carol; Kapur, Shitij. The Maudsley Prescribing Guidelines, Twelfth Edition. London: CRC Press; 2015.

Approximate equivalent doses of diazepam, oral 5mg: South African Medicines Formulary. 14th Edition. Division of Clinical Pharmacology. University of Cape Town. 2022.

[lxxiii]Benzodiazepine detoxification: Taylor, David; Paton, Carol; Kapur, Shitij. The Maudsley Prescribing Guidelines, Twelfth Edition. London: CRC Press; 2015.

Benzodiazepine detoxification: Baandrup L, Ebdrup BH, Rasmussen JØ, Lindschou J, Gluud C, Glenthøj BY. Pharmacological interventions for benzodiazepine discontinuation in chronic benzodiazepine users. Cochrane Database Syst Rev. 2018 Mar 15;3:CD011481. https://www.ncbi.nlm.nih.gov/pubmed/29543325

CHAPTER 16

RESPIRATORY DISORDERS

16.1 ASTHMA, ACUTE

J45.0-1/J45.8-9

DESCRIPTION

This is an emergency recognised by various combinations of:

- » wheeze
- » tightness of the chest
- » chest indrawing
- » breathlessness
- » respiratory distress
- » cough

In adults, bronchospasm is usually associated with asthma (where the bronchospasm is usually completely reversible) or chronic obstructive pulmonary disease ((COPD) where the bronchospasm is partially reversible).

The clinical picture of pulmonary oedema due to left ventricular heart failure may be similar to that of asthma. If patients >50 years of age present with asthma for the first time, consider pulmonary oedema due to left ventricular heart failure.

All PHC facilities must have peak expiratory flow rate (PEFR) meters as asthma cannot be correctly managed without measuring PEFR.

Recognition and assessment of severity of asthma attacks in adults

	Mild-Moderate	Severe	Life threatening
Oxygen saturation	>90%	<90%	<90%
Talks in	phrases	words	Unable to speak
Alertness	normal	Usually agitated	agitated, drowsy or confused
Respiratory rate	20–30 breaths/minute	often >30 breaths/minute	often >30 breaths/minute OR feeble effort
Wheeze	present	present	absent
Heart rate	100–120 beats/minute	>120 beats/minute	bradycardia
PEFR	>60% of predicted	<60% of predicted	<33% of expected or unable to blow

Note: PEFR is expressed as a percentage of the predicted normal value for the individual, or of the patient's personal best value obtained previously when on optimal treatment. (See PEF charts in Appendix V: Asthma monitoring.)

GENERAL MEASURES

Patients with moderate-severe or life-threatening asthma should ideally be closely monitored in a High Care- or Intensive Care Unit.

MEDICINE TREATMENT

See Appendix VI: Devices for Respiratory Conditions for guidance on inhaler, spacer and nebuliser device techniques.

Mild to moderate attacks

- Salbutamol 100 mcg metered-dose inhaler (MDI),
  - Salbutamol inhaler 400–1000 mcg (4-10 puffs) using a spacer if required and available. *LoE:IVb*[i]
  - Shake the inhaler between each puff.
  - If no relief, repeat every 20–30 minutes in the first hour.
  - Thereafter, repeat every 2–4 hours if needed.

  Note: Administering salbutamol via a spacer is as effective as, and cheaper than, using a nebuliser.

OR

- Salbutamol 0.5% (5 mg/mL), solution,
  - 1 mL (5 mg) salbutamol 0.5% solution made up to 4 mL with sodium chloride 0.9%, preferably delivered at a flow rate of 8 L/min with oxygen.
  - If no relief, repeat every 20–30 minutes in the first hour.
  - Thereafter, repeat every 2–4 hours if needed. *LoE:IVb*[ii]

PLUS

- Corticosteroids (intermediate-acting) e.g.: *LoE:IVb*[iii]
- Prednisone, oral, 40 mg immediately if patient known to have asthma/COPD.
  - Follow with prednisone, oral, 40 mg daily for 7 days.

Severe attacks

- Oxygen to keep oxygen saturation 93-95%.

AND

- Salbutamol 0.5% (5 mg/mL) nebuliser solution,
  - 1 mL (5 mg) salbutamol 0.5% solution, made up to 4 mL with sodium chloride 0.9%, preferably delivered at a flow rate of 8 L/min with oxygen.
  - If no relief, repeat every 20–30 minutes until PEF > 60% of predicted.
  - Once PEF > 60% of predicted, repeat every 2–4 hours if needed. *LoE:IVb*[iv]

OR

- Salbutamol, inhalation using a MDI, *LoE:IVb*[v]
  - Salbutamol 400–1000 mcg (4–10 puffs), up to 20 puffs, using a spacer.
  - Inhale 1 puff at a time. Allow for 6 breaths through the spacer between puffs.
  - If no relief, repeat every 20–30 minutes until PEF > 60% of predicted.
  - Once PEF > 60% of predicted, repeat every 2–4 hours if needed.

Note: Administering salbutamol via a spacer is as effective as, and cheaper than, using a nebuliser.

LoE:IVb[vi]

If response is poor after first salbutamol nebulisation/inhalation:

ADD

- Ipratropium bromide 0.5 mg/2ml; nebuliser solution. LoE:IIb[vii]
  - Ipratropium bromide, 2 mL (0.5 mg) added to salbutamol 1 mL (5 mg) solution and made up to 4 mL with sodium chloride 0.9%.
  - Administer every 20–30 minutes for 3 doses depending on clinical response.

OR

- Ipratropium bromide, MDI, 80–160 mcg (2–4 puffs), using a spacer every 20–30 minutes as needed for up to 3 hours. LoE:IIb[viii]

AND

Corticosteroids (intermediate-acting) e.g.: LoE:IVb[ix]

- Prednisone, oral, 40 mg immediately.
  - Follow with prednisone, oral, 40 mg daily for 7 days.

OR

In patients who cannot use oral therapy, are vomiting, or are suspected to have gastric atony from a severe asthma exacerbation: LoE:IVb[x]

- Hydrocortisone IM/slow IV, 100 mg 6 hourly.

Once oral medication can be taken, switch to:

- Corticosteroids (intermediate-acting) e.g.:
- Prednisone, oral, 40 mg daily for 7 days.

CAUTION
Avoid sedation of any kind.

Note: If poor response to treatment, consider alternate diagnosis and refer urgently.

<u>Life- threatening attacks</u>

- Oxygen, to keep oxygen saturation 93-95%.

AND

- Salbutamol 0.5% (5 mg/mL) with ipratropium bromide 0.5 mg/2mL nebuliser solution:
  - Salbutamol 0.5%, 2 mL (10 mg) plus ipratropium bromide, 2 mL (0.5 mg) every 20–30 minutes depending on clinical response for 4 doses over 2 hours.
  - Delivered at a flow rate of 8 L/min with oxygen.
  - If no relief, repeat every 20–30 minutes until asthma severity category moves from life-threatening to severe.

AND

- Parenteral corticosteroids (intermediate-acting), e.g.: LoE:IVb[xi]
- Hydrocortisone IM/slow IV, 100 mg 6 hourly.

Once oral medication can be taken, switch to:

- Corticosteroids (intermediate-acting) e.g.:
- Prednisone, oral, 40 mg daily for 7 days.

CAUTION
Avoid sedation of any kind.

Note: As clinical condition responds to treatment and severity improves to becomes severe but not life threatening, treat as per severe asthma exacerbation above.

Assessment of response in adults

	Response	No response
PEFR (if possible)	improvement by >20%	improvement by <20%
Respiratory rate	<20 breaths/ minute	>20 breaths/ minute
Speech	normal	impaired

Monitor response with PEF and clinical signs. Patients who fail to respond within 1 hour (symptomatic improvement and PEF >60% of predicted/personal best):

» Exclude upper airway obstruction/stridor, pneumothorax, and anaphylaxis.
» Discuss management with a specialist.
» Intubation and ventilator support may be required.
» If referral to another facility is required, the patient needs to be stabilised prior to transfer and transported by the appropriate level of transport – discuss with the referral centre.

In patients with a poor response:

ADD

- Magnesium sulfate, IV, (50 mg/kg, maximum dose 2 g) in 100 mL sodium chloride 0.9%, as a single dose, administered over 20 minutes.
  - Intravenous magnesium, single dose, has been shown to reduce the rate of hospitalisation. *LoE: I[xii]*

There is good evidence to recommend against the use of intravenous aminophylline in acute asthma as its use, together with high-dose nebulised ß$_2$-agonists, does not result in significant additional bronchodilation, and leads to a significant increase in toxicity (vomiting and dysrhythmias).

LoE: I[xiii]

Intercurrent bacterial respiratory infections

Bacterial infections are seldom present in acute exacerbations of asthma and yellow sputum production is usually related to presence of eosinophils. Antibiotics do not play a role in the management of asthma unless there is air space consolidation on CXR. See Section 16.6: Pneumonia, community acquired.

16.2 ASTHMA, CHRONIC PERSISTENT

J45.0-1/J45.8-9

DESCRIPTION

Asthma must be distinguished from chronic obstructive pulmonary disease, which is often mistaken for asthma. The history is a reliable diagnostic guideline and may be of value in assessing treatment response.

Asthma	COPD
» Young age onset, usually <20 years. » History of hay fever, eczema and/or allergies. » Family history of asthma. » Symptoms are intermittent with periods of normal breathing in between. » Symptoms are usually worse at night or in the early hours of the morning, during an upper respiratory tract infection, when the weather changes or when upset. » Increase 20% in PEF 10 minutes after receiving a ß$_2$-agonist. *LoE:II*[xiv]	» Older age onset, usually >40 years. » Symptoms slowly worsen over a long period of time. » Long history of daily/frequent cough, before the onset of shortness of breath. » Symptoms are persistent and not only at night or during the early morning. » History of heavy smoking (>20 cigarettes/day for ≥15 years), heavy cannabis use or previous TB. » Little improvement in PEF with ß$_2$-agonist.

GENERAL MEASURES

Patient education: including advice on smoking cessation.

Decrease exposure to triggers, e.g. house dust mite, pollens, grasses, pets, smoke, fumes, etc.

MEDICINE TREATMENT

Nocturnal symptoms of cough and wheeze, the need for bronchodilators more than twice a week, or PEF <80% of the patient's best value, indicates poor asthma control.

Patients with poorly controlled asthma need to step up their maintenance therapy as described below.

The Asthma Control Test®, a validated measure of clinical asthma control, can be completed by the patient (after initial instruction) at each visit to the clinic prior to consultation. A value of ≥20 suggests adequate asthma control (see Appendix V: Asthma monitoring).

See Appendix VI: Devices for Respiratory Conditions for guidance on inhaler, spacer and nebuliser device techniques.

A patient with poorly controlled asthma should be assessed for the following and identified problems addressed prior to stepping up therapy:

1) Correct inhaler technique should be demonstrated and checked regularly, as many asthmatic patients do not use their inhalers correctly.
2) Adherence to medication, especially the inhaled corticosteroid.
3) Ensure a spacer is being used for all MDIs and patient has been trained in its use.
4) Exposure to triggers of bronchospasm.
5) Use of medications that may aggravate asthma, e.g. NSAIDS.
6) Other medical conditions such as cardiac disease.
7) Treat allergic rhinitis (see Section 17.2: Rhinitis, allergic, persistent) and GORD (see Section 1.1.3: Gastro-oesophageal reflux disease (GORD) and dyspepsia, if present.

Asthma therapy

Inhaled corticosteroids (ICS) are the mainstay of treatment in asthma.

For patients with infrequent asthma symptoms < twice a month:

As reliever/rescue therapy:

- Short acting ß$_2$-agonists, e.g.:
- Salbutamol, MDI, 200 mcg, as needed.

AND LoE:III[xv]

- Inhaled corticosteroids, e.g.:
- Budesonide, inhalation, 200 mcg whenever salbutamol is taken.

In patients on protease inhibitors, beclomethasone is the preferred ICS as there are drug interactions between protease inhibitors and budesonide.

- Beclomethasone, inhalation, 200 mcg whenever salbutamol is taken.

LoE:III[xvi]

For patients with asthma symptoms ≥ twice a month:

As controller therapy:

- Inhaled corticosteroids, low dose, e.g.:
- Budesonide, inhalation, 200 mcg 12 hourly. LoE: I[xvii]
  - Well and stable after 6 months: can attempt to reduce budesonide dose to 200 mcg daily.
  - Dose adjustments may be required at change of seasons.

In patients on protease inhibitors, beclomethasone is the preferred ICS as there are drug interactions between protease inhibitors and budesonide.

- Beclomethasone, inhalation, 200 mcg 12 hourly for 6 months; reduced to 200 mcg daily once well and stable.

AND LoE:III[xviii]

As reliever/rescue therapy:

- Short acting ß$_2$-agonists, e.g.:
- Salbutamol, MDI, 200 mcg, 6 hourly as necessary.

For patients with asthma symptoms almost daily or waking due to asthma at least once a week:

- Long-acting β_2-agonist/corticosteroid combination inhaler, e.g.:
- Salmeterol/fluticasone, inhalation, 50/250 mcg 12 hourly.
  - Maximum dose: 50/500 mcg 12 hourly.
  - Well and stable for 6 months: step down to budesonide, inhaled, 200 mcg 12 hourly.

LoE: I[xix]

AND

As reliever/rescue therapy:

- Short acting ß$_2$-agonists, e.g.:
- Salbutamol, MDI, 200 mcg, 6 hourly as necessary.

In patients on protease inhibitors:

- Beclomethasone, inhalation, 400 mcg 12 hourly.

LoE:III[xx]

AND

- Formoterol, inhalation, 12 mcg 12 hourly.

Failure of above therapy:

While awaiting appointment with specialist.

ADD

- Corticosteroids (intermediate-acting) e.g.:
- Prednisone, oral, 10 mg daily.

  Note: Prednisone should not be used as maintenance therapy but only as a bridging step while awaiting review by specialist.

LoE: III

For short-term exacerbations in patients not responding to the above, while awaiting review with specialist:

- Corticosteroids (intermediate-acting) e.g.:
- Prednisone, oral, 40 mg daily for 10 days.

LoE: III

PATIENT AND CAREGIVER EDUCATION ON INHALER AND SPACER TECHNIQUES:

See Appendix VI: Devices for Respiratory Conditions for guidance on inhaler, spacer and nebuliser device techniques.

Spacer devices

Patients on step 3 therapy and above, and patients on step 1 and 2 who are unable to use aerosol inhalers correctly after adequate counselling, may benefit from the use of a spacer with metered dose inhalers.

16.3 BRONCHIECTASIS

J47

GENERAL MEASURES

Advice on early self-referral for suspected acute infections.
Physiotherapy: Regular chest clearance exercises (20 minutes morning and night) are the mainstay of therapy and must be emphasised and demonstrated to the patients, including cough and chest drainage techniques, and must be emphasised repetitively.

MEDICINE TREATMENT

Antimicrobial therapy

Antibiotic therapy in patients with bronchiectasis should only be used when there is either systemic evidence of sepsis such as pyrexia, or there is a history of increasing sputum purulence or volume. Antibiotic choices should be guided by sputum microscopy, culture and sensitivity. The number and duration of physiotherapy sessions should be increased.

Treatment may need to be prolonged for two weeks, depending on the extent of the bronchiectasis and the organisms suspected.

In patients otherwise stable and before culture results:

- Amoxicillin/clavulanic acid, oral, 875/125 mg 12 hourly for 10 days, or longer, depending on the response. A — LoE:III[xxi]

Severe penicillin allergy: (Z88.0)

- Azithromycin, oral, 500 mg daily for 10 days. W — LoE:IVb

More severely ill patients may require hospitalisation and initiation of parenteral antibiotic therapy.
Sputum microscopy, culture and sensitivity determination are indicated in all cases.

- Ceftriaxone 2 g, IV, daily, until patient apyrexial for 24 hours. W — LoE:III[xxii]

Follow with:

- Amoxicillin/clavulanic acid, oral, 875/125 mg 12 hourly. A — LoE:III[xxiii]

If Pseudomonas infection is confirmed on culture, change to: (B96.5)

- Ciprofloxacin, oral, 750 mg 12 hourly for 7 days. W

If penicillin allergic and unable to tolerate oral therapy: (Z88.0)
Management of these patients should be discussed with a specialist for possible referral and alternative parenteral therapy:

- Moxifloxacin, IV, 400 mg daily infused over 60 minutes. W — LoE:III[xxiv]

Switch to oral treatment once able to take orally:

- Moxifloxacin, oral, 400 mg daily to complete a total of 7 days of treatment with moxifloxacin i.e. total duration of 7 days for IV and oral combined. W

Subsequent antibiotic therapy should be based on results of sputum investigations. A sputum smear for Acid Fast Bacilli (AFB), followed by culture if positive, is recommended in patients with a poor response to antibiotics as patients with bronchiectasis are at increased risk for infection with non-tuberculous Mycobacteria which will not be detected by Xpert® MTB/RIF PCR assay. If tuberculosis is a consideration, also send a sputum for TB-NAAT testing.

Inhaled bronchodilators
Bronchodilators may be used, as for COPD, if airflow obstruction is present. There is no indication for inhaled corticosteroids in the management of bronchietasis.
Any asthmatic component (i.e. reversible obstruction) should be treated in the usual way, as for asthma. (See Sections 16.1: Asthma, acute, and 16.2: Asthma, chronic persistent.)
See Appendix VI: Devices for Respiratory Conditions for guidance on inhaler, spacer and nebuliser device techniques.

Prophylaxis (Z25.1)
- Annual influenza vaccine. See Section 9.2: Adult vaccination.

For frequent severe exacerbations, consult a specialist.

REFERRAL
» For exclusion of a possible foreign body.
» For assessment for surgical removal of a bronchiectatic segment.
» Major haemoptysis.

16.4 CHRONIC OBSTRUCTIVE PULMONARY DISEASE (COPD)
J43.0-2/J43.8-9/J44.0-1/J44.8-9

DESCRIPTION
COPD is characterised by persistent respiratory symptoms (dyspnoea, chronic cough and sputum production), and airflow limitation. Spirometry is required to diagnose COPD, where the post-bronchodilator FEV1/FVC ratio is <0.7. COPD is likely to worsen over time, even with optimal care.

Regular follow-up is necessary to monitor lung function, symptoms, exacerbations, co-morbidities, and the need for treatment regimen changes.

COPD can be graded on severity of symptoms and frequency of exacerbations to assist in treatment selection and to monitor treatment success:

LoE:III[xxv]

GOLD group	mMRC breathlessness score	Exacerbations/hospitalisations in past year
A	0–1	<2 exacerbations (and no hospitalisations)
B	≥2	<2 exacerbations (and no hospitalisations)
E	N/A	≥2 exacerbations (or ≥1 leading to hospitalisation)

Assess breathlessness using the mMRC dyspnoea scale:

Grade	Exacerbations in past year
0	Dyspnoea with strenuous exercise
1	Dyspnoea when hurrying on level ground or walking up a slight hill
2	Walks slower than people of same age group, due to dyspnoea
3	Stops for breath after walking 91m, or after a few minutes on level ground
4	Too breathless to leave the house, or dyspnoea when dressing/undressing

URL to the modified Medical Research Council (mMRC) dyspnoea scale calculator: https://www.mdcalc.com/mmrc-modified-medical-research-council-dyspnea-scale. *LoE:III*[xxvi]

GENERAL MEASURES

Patients with clinical COPD must undergo spirometry to confirm and grade the severity of obstruction.

Patients should be screened for ongoing smoking and advised to stop at each visit. Smoking cessation and avoidance of noxious respiratory particles should form the mainstay of management.

MEDICINE TREATMENT

Note: Correct inhaler technique should be demonstrated and checked regularly. See Appendix VI: Devices for Respiratory Conditions for guidance on inhaler, spacer and nebuliser device techniques.

Management of acute exacerbations

Progression of disease (measured by symptoms and deterioration in lung function) in COPD is variable, but is greater in patients who experience COPD exacerbations which are defined as:

» worsening of dyspnoea,
» increased cough,
» increased sputum production or purulence or,
» greater than usual day to day variability of symptoms.

Severe exacerbations are defined as being sufficiently severe to prompt use of an oral corticosteroid course and/or an antibiotic.

COPD exacerbations are not always associated with significant decreases in PEF or FEV_1, and are defined by symptoms and, when severe, measures of respiratory failure. Most are precipitated by viral and/or bacterial infection and are more common in winter.

Patients should be admitted if there is a marked increase in dyspnoea, symptoms disturb eating or sleeping, change in mental status or poor social circumstances. Causes of worsening symptoms other than an acute exacerbation of COPD such as cardiac failure, pulmonary embolus, or pneumonia must be considered**.**

If available, check blood gases for the presence of hypoxaemia and hypercapnia. In some patients with long-standing lung disease the drive to respiration switches from hypercapnia (increases in $PaCO_2$) to hypoxaemia (level of respiratory failure). In such patients, relief of hypoxaemia with uncontrolled oxygen therapy may result in hypoventilation, with consequent rise in $PaCO_2$ to dangerous levels and associated respiratory acidosis leading to coma and death. For this reason, hypoxaemia should be corrected using controlled use of supplemental oxygen, preferably starting with a nasal cannula 1-2 litres/minute.

If the patient's arterial $PaCO_2$ does not rise, the FiO_2 may be increased until a PaO_2 of 8 kPa (60 mmHg), or oxygen saturation of 90%, is reached. The FiO_2 must be reduced, or oxygen removed, if worsening hypercapnia occurs; these patients might require non-invasive ventilation or intubation for mechanical ventilation.

Where blood gas facilities are not readily available, the patient's clinical status should be reviewed regularly to check for increasing drowsiness, headache, or confusion, which may precede coma.

Where resources for mechanical ventilation are scarce, oxygen saturation targets for patients with long-standing COPD and limited effort tolerance may be relaxed if the patient is improving clinically.

- Salbutamol, 0.5% (5 mg/mL) nebuliser solution.
  - 1 mL (5 mg) salbutamol 0.5% solution, made up to 4 mL with sodium chloride 0.9%, preferably delivered at a flow rate of 6-8 L/min with oxygen.
  - Nebulise continuously (refill the nebuliser reservoir every 20 minutes).

<u>If a poor response to nebulised salbutamol:</u>

ADD

- Ipratropium bromide 0.5 mg (UDV) with the first refill of the nebuliser reservoir.
  - Patients who fail to respond within 1 hour must be discussed with a specialist. (Patients with COPD have fixed airway disease. Unlike asthmatics, PEF is not a reliable measure of disease.)

<u>Once clinically stabilised, nebulise with:</u>

- Salbutamol, 0.5% (5 mg/mL) nebuliser solution
  - 1 mL (5 mg) salbutamol 0.5% solution, made up to 4 mL with sodium chloride 0.9%, preferably delivered at a flow rate of 6-8 L/min with oxygen.
  - Repeat 4–6 hourly.

AND

- Corticosteroids (intermediate-acting), e.g.:
- Prednisone, oral, 40 mg immediately.
- Follow with: Prednisone, oral, 40 mg daily to complete 5 days.

LoE:I[xxvii]

OR

In patients who cannot use oral therapy:

- Hydrocortisone, IV, 100 mg 6 hourly until patient can take oral medication.

Once oral medication can be taken, follow with:

- Corticosteroids (intermediate-acting), e.g.:
- Prednisone, oral, 40 mg daily to complete 5 days of corticosteroids in total.
  - Monitor response and clinical signs.

LoE:I[xxviii]

Antibiotic therapy for acute exacerbations

LoE:IIIb[xxix]

Indications:

» Patients with increased sputum purulence AND either increased sputum volume or increased dyspnoea

OR

» Patients with a severe exacerbation (respiratory acidosis, severe dyspnoea, or persistent hypoxaemia despite supplemental oxygen).

- Amoxicillin/clavulanic acid, oral, 875/125 mg 12 hourly for 5 days. A

LoE:III[xxx]

Severe penicillin allergy: (Z88.0)

- Azithromycin, oral, 500 mg daily for 3 days. W

LoE:III[xxxi]

Chronic therapy

FOR ALL STAGES:

- Short acting β_2-agonists, e.g.:
- Salbutamol, MDI, 200 mcg 6 hourly as needed (educate on correct inhaler use - use a large volume spacer if inhaler technique remains poor).

GROUP B:

ADD

- Long acting β_2-agonist (LABA), e.g.:
- Formoterol, inhalation, 12 mcg 12 hourly.

LoE:III[xxxii]

LoE:I[xxxiii]

GROUP E (frequent exacerbations (≥2 per year)):

If blood eosinophils <0.1 cellsx10^9/L:

ADD

- Long acting β_2-agonist (LABA), e.g.:
- Formoterol, inhalation, 12 mcg 12 hourly.

LoE:I[xxxiv]

If blood eosinophils ≥0.1 cellsx10^9/L:

ADD

- LABA/ICS combination, e.g.:
- Salmeterol/fluticasone, inhalation, 50/250 mcg 12 hourly.

LoE:I[xxxv]

Note: Do not measure blood eosinophils while taking oral corticosteroids, as this may temporarily lower the eosinophil count.

Patients on protease inhibitors:
Replace LABA/ICS combination with:
- Beclomethasone, inhalation, 400 mcg 12 hourly.

AND LoE:III[xxxvi]
- Formoterol, inhalation, 12 mcg 12 hourly.

If inadequate control with above therapy:
- Theophylline, slow release, oral, 200 mg at night (Specialist consultation).
  - Ongoing use of theophylline should be re-evaluated periodically. If there is no benefit after 12 months, discontinue theophylline.

AND LoE:I[xxxvii]
Refer patients for additional assessment and management.

Corticosteroids
Oral corticosteroids are not recommended for stable COPD.
Pre-operative assessment for surgical procedures:
Patients with chronic lung disease are at an increased risk of post-operative pulmonary complications. Risk is increased with increasing severity of pulmonary disease, and with upper abdominal or thoracic surgery.
Patients undergoing elective surgery must be optimised pre-operatively by following the recommended treatment for their disease. Clinical assessment is generally sufficient, as further investigations such as spirometry, CXR and ABGs are reserved for patients with clinically severe disease/ unstable disease, or where the diagnosis is uncertain. COPD patients should be wheeze free and without dyspnoea on moderate exertion (carrying shopping walking up a flight of stairs), or a history of frequent exacerbations. As COPD is a disease characterised by fixed airway obstruction, some patients may have continuous wheezing and will require further pre-operative assessment. Peri-operative oral corticosteroids may be used to gain optimal control but are not advocated for routine use:
- Corticosteroids (intermediate-acting), e.g.:
- Prednisone, oral, 30 mg daily for not longer than 5 days.

AND LoE:III
Inhaled therapy must be continued and may be administered via nebulisation peri-operatively:
- Short acting β_2-agonists, e.g.:
- Salbutamol MDI, 200 mcg, 30 minutes pre-intubation. LoE:III

Prophylaxis (Z25.1)
- Annual influenza vaccination. See Section 9.2: Adult vaccination.

REFERRAL

» Assessment for long-term home-based oxygen therapy, if COPD with PaO_2 <7.3 kPa (55 mmHg) and non-smoker for at least 3 months.
» Recent onset of respiratory failure or signs of cor pulmonale.
» Symptoms that appear disproportionate to the level of airflow obstruction, as judged by spirometry or clinical evaluation (absence of hyperinflation or unusual pattern of symptoms).
» Onset <40 years of age.
» COPD with a history of little or no smoking.
» Recurrent exacerbations, i.e. ≥2 per year.
» Failure to respond to treatment.

16.5 LUNG ABSCESS

J85.0-3

GENERAL MEASURES

Physiotherapy and regular emphasis on postural drainage is essential for management.
Instruct patient to do chest clearance exercises (taught by a physiotherapist where possible) for at least 20 minutes, 6 hourly.
Nutritional support.

MEDICINE TREATMENT

- Amoxicillin/clavulanic acid, IV, 1.2 g 8 hourly, until patient apyrexial for 24 hours. A

Follow with:

- Amoxicillin/clavulanic acid, oral, 875/125 mg 12 hourly. A LoE:III

Severe penicillin allergy: (Z88.0)

- Moxifloxacin, IV, 400 mg daily, until patient apyrexial for 24 hours. W

Follow with:

- Moxifloxacin, oral, 400 mg daily. W LoE:II[xxxviii]

Duration of therapy
Usually 4-6 weeks – monitor with repeat CXR every 1-2 weeks, which should show disappearance of air-fluid level and reduction in size of abscess.

REFERRAL

» No response to treatment.
» CXR not resolving or worsening.
» Complications, such as empyema or severe haemoptysis.

16.6 PNEUMONIA, COMMUNITY ACQUIRED

J13/J14/J15.0-9/J16.0/J16.8/J18.0-2/J18.8-9

DESCRIPTION

Pneumonia is an acute infection of the lung parenchyma. Early appropriate antibiotic therapy decreases mortality. The decision to hospitalise a patient and choice of initial antibiotic therapy is guided by age, comorbid diseases (such as HIV infection, diabetes or chronic respiratory disease), and severity. Socioeconomic circumstances should form part of the clinical assessment when deciding if a patient is suitable for outpatient treatment.

GENERAL MEASURES

Diagnosis: LoE:III[xxxix]

Clinical features include cough, fever, tachypnoea, and signs of consolidation on chest examination.

CXR almost invariably shows a focal area of opacification or consolidation. However, empiric antibiotic therapy can be considered for severely ill, hospitalised patients with suspected pneumonia, and a negative CXR. Pneumonia may be excluded if a repeat CXR after 24-48 hours still shows no opacification. Diffuse, bilateral, interstitial infiltrates in a patient with HIV infection and hypoxaemia is suggestive of *Pneumocystis jirovecii* pneumonia.

All patients should be offered HIV testing, as HIV infection is associated with a markedly increased risk of bacterial pneumonia.

Even in typical cases of pneumonia, exclude tuberculosis by sending sputum for Xpert® MTB/RIF Ultra.

A follow-up CXR should be done 4–6 weeks after completion of therapy in patients >50 years of age, or if symptoms persist. LoE:III[xl]

Follow-up CXRs are indicated earlier only when complications are suspected, e.g. empyema, abscess, or pneumothorax.

MEDICINE TREATMENT

- Oxygen, if saturation <94%. LoE:I[xli]

Adequate analgesia for pleuritic chest pain, if present. See Section 25.2.1: Medical conditions associated with severe pain.

Antimicrobial therapy

Duration of antibiotic therapy is guided by clinical response, but should be 5-7 days, with a minimum of 7 days for MRSA or Pseudomonas.

Longer duration of antibiotic therapy is recommended for:

» identified pathogen that is not susceptible to initial empiric therapy,
» extrapulmonary infection (e.g. meningitis or endocarditis),
» empyema, lung abscess or necrotizing pneumonia,
» unusual organism present. LoE:I[xlii]

Prolonged fever and clinical signs may be due to unrecognised TB, complications (such as empyema), incorrect choice of antibiotic (e.g. atypical bacteria), or an underlying bronchial obstruction (foreign body or carcinoma). These patients should be further investigated.

Community-acquired pneumonia without features of severe pneumonia (see below for definition) and without co-morbidity and in patients <65 years of age:

- Ampicillin, IV, 1 g 6 hourly. A

In haemodynamically stable patients with respiratory rate <25 breaths/min and temperature <37.8°C, switch to:

- Amoxicillin, oral, 1 g 8 hourly for 5 days i.e. total duration of 5 days for IV and oral antibiotics combined. A LoE:I[xliii]

Severe penicillin allergy: (Z88.0)

- Moxifloxacin, oral, 400 mg daily for 5 days. W

If response is poor after 48 hours, exclude TB and consider atypical bacterial pneumonia, which requires treatment with a macrolide.

Community-acquired pneumonia without features of severe pneumonia (see below for definition) in patients >65 years of age or co-morbidity (e.g. COPD, HIV, cardiac failure, diabetes):

- Ceftriaxone, IV, 2 g daily. W LoE:I[xliv]

In haemodynamically stable patients with respiratory rate <25 breaths/min and temperature <37.8°C, switch to:

- Amoxicillin/clavulanic acid, oral, 875/125 mg 12 hourly for 5 days. A LoE:III[xlv]

Severe penicillin allergy: (Z88.0)

- Moxifloxacin, oral, 400 mg daily for 5 days. W

If response is poor after 48 hours, exclude TB and consider atypical bacterial pneumonia, which requires treatment with a macrolide.

Severe pneumonia (cyanosis, confusion, hypotension or respiratory rate >30 breaths/min):

- Ceftriaxone, IV, 2 g daily. W

Mechanical ventilation may be required (refer to a centre, if needed).

In haemodynamically stable patients with respiratory rate <25 breaths/min and temperature <37.8°C, switch to:

- Amoxicillin/clavulanic acid, oral, 875/125 mg 12 hourly for 5 days. A LoE:III[xlvi]

AND

- Azithromycin, 500 mg, slow IV (minimum infusion duration of 60 minutes) daily for 3 days. W

LoE:III[xlvii]

Severe penicillin allergy: (Z88.0)

- Moxifloxacin, IV, 400 mg daily. W

In haemodynamically stable patients with respiratory rate <25 breaths/min and temperature <37.8°C, switch to:

- Moxifloxacin, oral, 400 mg daily for 5 days. W

Note: There is no need to add a macrolide as moxifloxacin has adequate cover for atypical bacteria.

HIV infected with bilateral diffuse interstitial infiltrates on CXR:
Clinical presentation includes a dry cough of <12 weeks' duration and significant tachypnoea.

Treat as *Pneumocystis jirovecii* pneumonia (exclude TB) - see Section 10.2.9: Pneumocystis pneumonia.

16.7 PNEUMONIA, ASPIRATION

J69.0-1/J69.8

DESCRIPTION

Following aspiration, a patient may develop pneumonitis or pneumonia. Aspiration pneumonitis develops within hours of the aspiration event and is more common in previously healthy people who aspirate gastric acid. Antibiotics will not benefit these patients unless infection is present.
Pneumonia following aspiration of gastric contents and/or commensal organisms from the oropharynx usually occurs in debilitated patients and presents with symptoms and signs of community-acquired pneumonia. However, it may also have a more indolent onset and is more frequently complicated by lung abscess or empyema.
There may be solid (food) particles or other foreign bodies aspirated. The organisms involved are polymicrobial, i.e. Gram-positive and anaerobes. Aspiration pneumonia should be suspected in patients with episodic or prolonged decreased level of consciousness, e.g. in alcoholics, drug overdoses, epileptics, strokes, or those with swallowing problems.

MEDICINE TREATMENT

Antimicrobial therapy

Treatment duration: Continue therapy until there are no features of sepsis.

- Amoxicillin/clavulanic acid, IV, 1.2 g 8 hourly, until patient is apyrexial and stable for 24 hours. A

Follow with:

- Amoxicillin/clavulanic acid, oral, 875/125 mg 12 hourly. A

LoE:III

Severe penicillin allergy: (Z88.0)

- Moxifloxacin, IV, 400 mg daily, until patient is apyrexial for 24 hours. W

Follow with:

- Moxifloxacin, oral, 400 mg daily. W

LoE:II[xlviii]

If **nosocomial infection** is present (develops >48 hours post admission), see Section 9.1.3: Hospital-acquired pneumonia (HAP) and ventilator-associated pneumonia (VAP).

REFERRAL

» Hypoxaemia non-responsive to facemask oxygen.
» Suspected foreign body aspiration.
» Suspected chemical aspiration pneumonia.
» Non-resolving pneumonia.

16.8 EMPYEMA

J86.0/J86.9

DESCRIPTION

Pus in the pleural cavity and/or bacteria present in a pleural effusion. An empyema is always secondary to another process, e.g. pneumonia (especially aspiration pneumonia), lung abscess, tuberculosis, bacteraemia, penetrating chest wall, or oesophageal injury.

GENERAL MEASURES

Aspirate and analyse all pleural effusions.
A parapneumonic effusion should be distinguished from an empyema by biochemical analysis, fluid microscopy and culture (MCS) – tube drainage is indicated if the aspirated fluid pH is <7.2, shows bacteria on MCS, or is purulent. The primary management of empyema is early and complete drainage by insertion of an intercostal drain to prevent long-term complications.

MEDICINE TREATMENT

Antimicrobial therapy

If an empyema occurs due to a complication of pneumonia, antimicrobial therapy should be prescribed as guided in Section 16.6: Pneumonia, community acquired (the duration of therapy should be prolonged until drainage is complete).

If not a complication of pneumonia:

- Amoxicillin/clavulanic acid, IV, 1.2 g 8 hourly, until patient is apyrexial for 24 hours. A

Follow with:

- Amoxicillin/clavulanic acid, oral, 875/125 mg 12 hourly. A

LoE:III

Continue treatment until drainage is complete.

Severe penicillin allergy (and not a complication of pneumonia): (Z88.0)

- Moxifloxacin, IV, 400 mg daily, until patient is apyrexial for 24 hours. W

Follow with:

LoE:III

- Moxifloxacin, oral, 400 mg daily. W

Continue treatment until drainage is complete.

REFERRAL

» Loculated empyema or inadequate drainage.
» Chronic empyema with pleural thickening and restrictive lung disease, for consideration for surgical decortication.

16.9 TUBERCULOSIS, PULMONARY

A15.0-3/A15.7-8/A16.0-2/A16.4/A16.7-9 + (B20.0)
* Notifiable medical condition.

Tuberculosis (TB) treatment guidelines are updated regularly. This STG should be read in conjunction with the most recent National Tuberculosis Control Programme guidelines.

DESCRIPTION

A chronic, granulomatous infection of the lungs caused by *M. tuberculosis*. Pulmonary tuberculosis is a serious health problem in South Africa and is exacerbated by HIV and multidrug resistant tuberculosis (MDR-TB).

Note: All patients with TB disease should be notified.

Diagnosis

Molecular tests (TB nucleic acid amplification tests, TB-NAAT) are used for the diagnosis of *M. tuberculosis* and the identification of drug-resistant organisms. While some TB-NAAT assays test for both rifampicin and isoniazid resistance, Xpert® MTB/RIF Ultra, a type of TB-NAAT, only tests for rifampicin resistance. Refer to PHC EML Section 17.4.1 Pulmonary TB in adults for guidance on sputum sampling and interpretation of results relating to TB-NAAT assays.

The diagnosis of pulmonary TB in adults is made on a positive TB-NAAT on sputum. In some patients, especially HIV-infected patients, TB-NAAT is not an adequate 'rule out' test. PLHIV who have features of TB but are TB-NAAT negative require further investigation and may need empiric anti-tuberculosis therapy while awaiting TB cultures.

Patients who have previously completed TB treatment (especially within the last 2 years) may still test TB-NAAT positive in the absence of active disease. TB should be confirmed on culture in this setting.

All patients who are TB-NAAT positive require further sputum to be sent for AFB to allow for monitoring of treatment. TB-NAAT should not be used for monitoring.

All TB patients must be screened for HIV. PLHIV with concomitant TB are eligible for cotrimoxazole prophylaxis, regardless of CD4 count.

Sputum induction with nebulised sodium chloride 5% should be attempted for patients unable to spontaneously produce sputum. A wide bore needle (e.g. 18G) aspiration for TB-NAAT should be done in patients with suspected TB lymphadenitis. *LoE:III[xlix]*

Urine lipoarabinomannan (LAM) is a good "rule-in" diagnostic test for:
1) PLHIV with CD4 ≤200 cells/μL who have signs and symptoms of pulmonary and/or extrapulmonary TB, and *LoE:I[l]*
2) PLHIV who are seriously ill.

MEDICINE TREATMENT

All patients with active TB who are TB-NAAT positive and rifampicin sensitive should receive intensive phase therapy for 2 months and 4 months of continuation phase treatment (see table below). Patients who are at risk of having resistant TB (e.g. previous episode of TB treatment, prisoners, and health care workers) should have sputum sent to exclude INH mono resistance if the particular TB-NAAT test in use for pulmonary specimens does not already test for this.

National tuberculosis control programme guidelines
Fixed dose drug combinations available:

RH – 150/75 mg	RH – 300/150 mg
RHZE – 150/75/400/275 mg	
R – Rifampicin Z – Pyrazinamide	H – Isoniazid (INH) E – Ethambutol

Treatment for known or presumed drug sensitive TB:

Pre-treatment body weight	Two months initial phase	Four months continuation phase	
	RHZE (150/75/400/275)	RH (150/75)	RH (300/150)
30–37 kg	2 tablets	2 tablets	
38–54 kg	3 tablets	3 tablets	
55–70 kg	4 tablets		2 tablets
71 kg and over	5 tablets		2 tablets

INH may result in the development of a peripheral neuropathy due to drug-induced pyridoxine deficiency. Prophylactic pyridoxine supplementation is recommended in patients on INH that are at high risk of peripheral neuropathy (e.g. HIV, diabetes, alcoholics).

- Pyridoxine 25 mg, oral, daily for duration of INH-containing TB therapy.

Close contacts of TB patients (particularly children <5 years of age) should be screened and managed as per National TB Guidelines.

16.10 TUBERCULOSIS, PLEURAL (TB PLEURISY)

A16.5 + (B20.0)

DESCRIPTION

TB pleurisy may present with a few weeks of pleuritic pain; often associated with a dry cough, fever, night sweats, weight loss, and, with large effusions, progressive shortness of breath.

Diagnosis

It is essential to perform a diagnostic tap of pleural effusions confirmed on CXR.

Although a definite diagnosis can only be made by demonstrating the organisms on smear or culture, or on histology of a pleural biopsy, the presence of a lymphocytic exudate on pleural fluid analysis is adequate to start empiric TB therapy in areas with a high TB burden, particularly if the patient has HIV infection.

All patients started on empiric TB therapy for pleural TB must be followed up closely; failure to respond as expected must prompt investigations to exclude other causes. Once TB therapy is started, signs and symptoms should resolve within 2 weeks. Radiographic improvement is usually evident by 6 weeks, but complete resorption can take up to 4 months. However, pleural thickening may persist. A pleural biopsy at initial presentation is strongly recommended for the following patients: >50 years of age, suspected malignancy, or those with atypical TB symptoms.

Treatment is as for pulmonary TB (see Section 16.9: Tuberculosis, pulmonary).

Note: Total drainage by aspiration or under-water tube is not needed. For large effusions that cause dyspnoea, drain a maximum of 1 litre at a time. However, note that a TB pleural empyema must be drained by intercostal tube.

REFERRAL

» Non-resolving effusions. Suspect an incorrect diagnosis of TB pleurisy if the effusion does not improve on the CXR after 3 months of treatment, or if the patient deteriorates.
» Loculated TB empyema, not resolving after intercostal underwater tube drainage and needing assessment for surgical drainage.
» Bronchopleural fistula, not resolving after 6 weeks.

16.11 DRUG-RESISTANT TB

16.11.1 ISONIAZID MONORESISTANT TB

A15.0-9/A16.0-5/A16.7-9/A17.0-1/A17.8-9/A18.0-8/A19.0-2/A19.8-9 + (B20.0) + (U50.00-01/U50.10-11)

Isoniazid monoresistant TB is TB disease caused by *M. tuberculosis* complex that is resistant to isoniazid but susceptible to rifampicin.

MEDICINE TREATMENT

Confirmed isoniazid monoresistant TB:

- RHZE at standard dosing,

AND

- Levofloxacin, oral, daily:
  - 30–45 kg: 750 mg
  - ≥46 kg: 1000 mg

Confirmed isoniazid monoresistant TB AND contraindication to isoniazid:

- Rifampicin, oral, 10 mg/kg daily.

AND

- Ethambutol, oral, 15 mg/kg daily.

AND

- Pyrazinamide, oral, 25 mg/kg daily.

AND

- Levofloxacin, oral, daily:
  - 30–45kg: 750 mg
  - ≥46kg: 1000 mg

Treatment should be given for at least 6 months.

16.11.2 RIFAMPICIN RESISTANT, Pre-XDR and XDR TB

A15.0-9/A15.7-8/A16.0-5/A16.7-9/A17.0-1/A17.8-9/A18.0-7/A18.8/A19.0-2/ A19.8-9 + (B20.0) + (U50.00-01/U50.20-21/U50.30-31)

Never treat for drug-resistant TB without laboratory confirmation, either by molecular or phenotypic (culture and sensitivity) results.

DESCRIPTION

Rifampicin resistant tuberculosis (RR-TB) is diagnosed when there is resistance of *M. tuberculosis* to rifampicin, with or without resistance to other anti-TB drugs. RR-TB is diagnosed exclusively on culture and sensitivity assays or TB nucleic acid amplification tests (TB-NAAT). While some TB-NAAT assays test for both rifampicin and isoniazid resistance, Xpert® MTB/RIF Ultra, a type of TB-NAAT, only tests for rifampicin resistance. However, rifampicin resistance detected by Xpert® MTB/RIF Ultra is sufficient

to start a patient on RR treatment, pending confirmation of RR-TB by line probe assay.

Pre XDR-TB is TB disease caused by a strain of *M. tuberculosis* that is resistant to rifampicin (with or without INH resistance) and at least one fluoroquinolone (either levofloxacin or moxifloxacin). Extensively drug-resistant TB (XDR-TB) is TB disease caused by a strain of *M. tuberculosis* that is resistant to rifampicin AND at least one fluoroquinolone (levofloxacin or moxifloxacin) AND either bedaquiline or linezolid. Confirmation of pre XDR- and XDR-TB requires line probe assay and drug susceptibility testing.

GENERAL MEASURES

Screen all close contacts for signs and symptoms to detect early disease.

MEDICINE TREATMENT

Drug resistant TB prophylaxis

The effectiveness of preventive therapy in adults exposed to drug resistant TB bacteria is not currently known. Consult a specialist for management.

RR-TB and Pre XDR-TB treatment

Consult the most recent national drug-resistant TB programme guidelines. Treatment for 6–18 months is required. *LoE:IVbI[ii]*

Management of drug-resistant TB should be conducted in dedicated drug-resistant TB clinics and hospitals with appropriate infection control measures.

XDR-TB treatment

Patients with XDR-TB should be discussed with the National Clinical Advisory Committee (Email: NCAC@witshealth.co.za) and referred to a TB hospital for an individualised regimen of at least 4 effective medicines, based on susceptibility tests and treatment history. Infection control to prevent airborne transmission is essential to prevent nosocomial transmission.

References:

[i] Salbutamol MDI (dose in adults and children): SAMF 14th Edition

[ii] Salbutamol nebulisation (adults): National Department of Health, Essential Drugs Programme: Adult Hospital Level STGs and EML, 2019. http://www.health.gov.za/

[iii] Corticosteroids (intermediate-acting): National Department of Health, Essential Drugs Programme: Adult Hospital level STGs and EML, 2019. http://www.health.gov.za/

Corticosteroids (intermediate-acting): South African Medicines Formulary. 12th Edition. Division of Clinical Pharmacology. University of Cape Town, 2016.

[iv] Salbutamol nebulisation (adults): National Department of Health, Essential Drugs Programme: Adult Hospital Level STGs and EML, 2019. http://www.health.gov.za/

[v] Salbutamol MDI (adults): National Department of Health, Essential Drugs Programme: Adult Hospital Level STGs and EML, 2019. http://www.health.gov.za/

[vi] Salbutamol MDI (adults): Rodrigo C, Rodrigo G. Salbutamol treatment of acute severe asthma in the ED: MDI versus hand-held nebulizer. Am J Emerg Med. 1998 Nov16(7):637-42. https://www.ncbi.nlm.nih.gov/pubmed/9827736

Salbutamol MDI (adults): National Department of Health, Essential Drugs Programme: Adult Hospital Level STGs and EML, 2019. http://www.health.gov.za/

[vii] Ipratropium bromide 0.5 mg nebulisation (adults): Global initiative for asthma (GINA) Guidelines, 2018. http://ginasthma.org/

[viii] Ipratropium bromide MDI (adults): Global initiative for asthma (GINA) Guidelines, 2018. http://ginasthma.org/

[ix] Corticosteroids (intermediate-acting): National Department of Health, Essential Drugs Programme: Adult Hospital level STGs and EML, 2019. http://www.health.gov.za/

Corticosteroids (intermediate-acting): South African Medicines Formulary. 12th Edition. Division of Clinical Pharmacology. University of Cape Town, 2016.

[x] Corticosteroids (intermediate-acting): National Department of Health, Essential Drugs Programme: Adult Hospital level STGs and EML, 2019. http://www.health.gov.za/

Corticosteroids (intermediate-acting): South African Medicines Formulary. 12th Edition. Division of Clinical Pharmacology. University of Cape Town, 2016.

[xi] Corticosteroids (intermediate-acting): National Department of Health, Essential Drugs Programme: Adult Hospital level STGs and EML, 2019. http://www.health.gov.za/

Corticosteroids (intermediate-acting): South African Medicines Formulary. 12th Edition. Division of Clinical Pharmacology. University of Cape Town, 2016.

[xii] Magnesium sulfate: Kew KM, Kirtchuk L, Michell CI. Intravenous magnesium sulfate for treating adults with acute asthma in the emergency department. Cochrane Database Syst Rev.2014 May 28;5:CD010909.http://www.ncbi.nlm.nih.gov/pubmed/24865567

Magnesium sulfate: Goodacre S, Cohen J, Bradburn M, Gray A, Benger J, Coats T; 3Mg Research Team. Intravenous or nebulised magnesium sulfate versus standard therapy for severeacute asthma (3Mg trial): a double-blind, randomised controlled trial. LancetRespir Med. 2013 Jun;1(4):293-300.http://www.ncbi.nlm.nih.gov/pubmed/24429154

[e] Aminophylline: Nair P, Milan SJ, Rowe BH. Addition of intravenous aminophylline to inhaled beta(2)-agonists in adults with acute asthma. Cochrane Database Syst Rev. 2012 Dec 12;12:CD002742.http://www.ncbi.nlm.nih.gov/pubmed/23235591

[xiv] Treatment response with SABA: Global Initiative for Asthma. Global Strategy for Asthma Management and Prevention, 2019. http://www.ginasthma.org/

[xv] Low-dose ICS with SABA MDI (Rescue use): Global Initiative for Asthma. Global Strategy for asthma management and prevention, 2019. http://www.ginasthma.org/

Low-dose ICS with SABA MDI (Rescue use): Reddel HK, FitzGerald JM, Bateman ED, Bacharier LB, Becker A, Brusselle G, Buhl R, Cruz AA, Fleming L, Inoue H, Ko FW, Krishnan JA, Levy ML, Lin J, Pedersen SE, Sheikh A, Yorgancioglu A, Boulet LP. GINA 2019: a fundamental change in asthma management: Treatment of asthma with short-acting bronchodilators alone is no longer recommended for adults and adolescents. Eur Respir J. 2019 Jun 27;53(6). https://www.ncbi.nlm.nih.gov/pubmed/31249014

Low-dose ICS with SABA MDI (Rescue use): Papi A, Canonica GW, Maestrelli P, Paggiaro P, Olivieri D, Pozzi E, Crimi N, Vignola AM, Morelli P, Nicolini G, Fabbri LM; BEST Study Group. Rescue use of beclomethasone and albuterol in a single inhaler for mild asthma. N Engl J Med. 2007 May 17;356(20):2040-52. https://www.ncbi.nlm.nih.gov/pubmed/17507703

Low-dose ICS with SABA MDI (Rescue use): Suissa S, Ernst P, Benayoun S, Baltzan M, Cai B. Low-dose inhaled corticosteroids and the prevention of death from asthma. N Engl J Med. 2000 Aug 3;343(5):332-6. https://www.ncbi.nlm.nih.gov/pubmed/10922423

Low-dose ICS with SABA MDI (Rescue use): Suissa S, Ernst P, Kezouh A. Regular use of inhaled corticosteroids and the long term prevention of hospitalisation for asthma. Thorax. 2002 Oct;57(10):880-4. https://www.ncbi.nlm.nih.gov/pubmed/12324675

Low-dose ICS with SABA MDI (Rescue use):Pauwels RA, Pedersen S, Busse WW, Tan WC, Chen YZ, Ohlsson SV, Ullman A, Lamm CJ, O'Byrne PM; START Investigators Group. Early intervention with budesonide in mild persistent asthma: a randomised, double-blind trial. Lancet. 2003 Mar 29;361(9363):1071-6. https://www.ncbi.nlm.nih.gov/pubmed/12672309

Low-dose ICS with SABA MDI (Rescue use): Reddel HK, Busse WW, Pedersen S, Tan WC, Chen YZ, Jorup C, Lythgoe D, O'Byrne PM. Should recommendations about starting inhaled corticosteroid treatment for mild asthma be

based on symptom frequency: a post-hoc efficacy analysis of the START study. Lancet. 2017 Jan 14;389(10065):157-166. https://www.ncbi.nlm.nih.gov/pubmed/27912982

[xvi] Inhaled corticosteroids (Patients on protease inhibitors): Kedem E, Shahar E, Hassoun G, Pollack S. Iatrogenic Cushing's syndrome due to coadministration of ritonavir and inhaled budesonide in an asthmatic human immunodeficiency virus infected patient. J Asthma. 2010 Sep;47(7):830-1. https://www.ncbi.nlm.nih.gov/pubmed/20653496

Inhaled corticosteroids (Patients on protease inhibitors): Frankel JK, Packer CD. Cushing's syndrome due to antiretroviral-budesonide interaction. Ann Pharmacother. 2011 Jun;45(6):823-4. https://www.ncbi.nlm.nih.gov/pubmed/21558486

Inhaled corticosteroids (Patients on protease inhibitors): Blondin MC, Beauregard H, Serri O. Iatrogenic Cushing syndrome in patients receiving inhaled budesonide and itraconazole or ritonavir: two cases and literature review. Endocr Pract. 2013 Nov-Dec;19(6):e138-41. https://www.ncbi.nlm.nih.gov/pubmed/23807527

Inhaled corticosteroids (Patients on protease inhibitors): Yoganathan K, David L, Williams C, Jones K. Cushing's syndrome with adrenal suppression induced by inhaled budesonide due to a ritonavir drug interaction in a woman with HIV infection. Int J STD AIDS. 2012 Jul;23(7):520-1. https://www.ncbi.nlm.nih.gov/pubmed/22844010

[xvii] Inhaled corticosteroids: Suissa S, Ernst P, Benayoun S, Baltzan M, Cai B. Low-dose inhaled corticosteroids and the prevention of death from asthma. N Engl J Med. 2000 Aug 3;343(5):332-6. https://www.ncbi.nlm.nih.gov/pubmed/10922423

Inhaled corticosteroids: Busse WW, Pedersen S, Pauwels RA, Tan WC, Chen YZ, Lamm CJ, O'Byrne PM; START Investigators Group. The Inhaled Steroid Treatment As Regular Therapy in Early Asthma (START) study 5-year follow-up: effectiveness of early intervention with budesonide in mild persistent asthma. J Allergy ClinImmunol. 2008May;121(5):1167-74.http://www.ncbi.nlm.nih.gov/pubmed/18405951

Inhaled corticosteroids: Reddel HK, Busse WW, Pedersen S, Tan WC, Chen YZ, Jorup C, Lythgoe D, O'Byrne PM. Should recommendations about starting inhaled corticosteroid treatment for mild asthma be based on symptom frequency: a post-hoc efficacy analysis of the START study. Lancet. 2017 Jan 14;389(10065):157-166. https://www.ncbi.nlm.nih.gov/pubmed/27912982

Inhaled corticosteroids: Global Initiative for Asthma. Global Strategy for Asthma Management and Prevention, 2019. http://www.ginasthma.org/

[xviii] Inhaled corticosteroids (Patients on protease inhibitors): Kedem E, Shahar E, Hassoun G, Pollack S. Iatrogenic Cushing's syndrome due to coadministration of ritonavir and inhaled budesonide in an asthmatic human immunodeficiency virus infected patient. J Asthma. 2010 Sep;47(7):830-1. https://www.ncbi.nlm.nih.gov/pubmed/20653496

Inhaled corticosteroids (Patients on protease inhibitors): Frankel JK, Packer CD. Cushing's syndrome due to antiretroviral-budesonide interaction. Ann Pharmacother. 2011 Jun;45(6):823-4. https://www.ncbi.nlm.nih.gov/pubmed/21558486

Inhaled corticosteroids (Patients on protease inhibitors): Blondin MC, Beauregard H, Serri O. Iatrogenic Cushing syndrome in patients receiving inhaled budesonide and itraconazole or ritonavir: two cases and literature review. Endocr Pract. 2013 Nov-Dec;19(6):e138-41. https://www.ncbi.nlm.nih.gov/pubmed/23807527

Inhaled corticosteroids (Patients on protease inhibitors): Yoganathan K, David L, Williams C, Jones K. Cushing's syndrome with adrenal suppression induced by inhaled budesonide due to a ritonavir drug interaction in a woman with HIV infection. Int J STD AIDS. 2012 Jul;23(7):520-1. https://www.ncbi.nlm.nih.gov/pubmed/22844010

[xix]Long-acting β2-agonist/corticosteroid combination inhaler: Walters EH, Gibson PG, Lasserson TJ, Walters JA. Long-acting beta2-agonists for chronic asthma in adults and children where background therapy contains varied or no inhaled corticosteroid. Cochrane Database Syst Rev. 2007 Jan24;(1):CD001385. http://www.ncbi.nlm.nih.gov/pubmed/17253458

Long-acting β2-agonist/corticosteroid combination inhaler: Global Initiative for Asthma. Global Strategy for Asthma Management and Prevention, 2019. http://www.ginasthma.org/

Long-acting β2-agonist/corticosteroid combination inhaler: South African Medicines Formulary. 12th Edition. Division of Clinical Pharmacology. University of Cape Town. 2016.

[xx] Inhaled corticosteroids (Patients on protease inhibitors): Kedem E, Shahar E, Hassoun G, Pollack S. Iatrogenic Cushing's syndrome due to coadministration of ritonavir and inhaled budesonide in an asthmatic human immunodeficiency virus infected patient. J Asthma. 2010 Sep;47(7):830-1. https://www.ncbi.nlm.nih.gov/pubmed/20653496

Inhaled corticosteroids (Patients on protease inhibitors): Frankel JK, Packer CD. Cushing's syndrome due to antiretroviral-budesonide interaction. Ann Pharmacother. 2011 Jun;45(6):823-4. https://www.ncbi.nlm.nih.gov/pubmed/21558486

Inhaled corticosteroids (Patients on protease inhibitors): Blondin MC, Beauregard H, Serri O. Iatrogenic Cushing syndrome in patients receiving inhaled budesonide and itraconazole or ritonavir: two cases and literature review. Endocr Pract. 2013 Nov-Dec;19(6):e138-41. https://www.ncbi.nlm.nih.gov/pubmed/23807527

Inhaled corticosteroids (Patients on protease inhibitors): Yoganathan K, David L, Williams C, Jones K. Cushing's syndrome with adrenal suppression induced by inhaled budesonide due to a ritonavir drug interaction in a woman with HIV infection. Int J STD AIDS. 2012 Jul;23(7):520-1. https://www.ncbi.nlm.nih.gov/pubmed/22844010

[xxi] Amoxicillin/clavulanic acid, oral: Pasteur MC, Bilton D, Hill AT; British Thoracic Society Bronchiectasis non-CF Guideline Group. British Thoracic Society guideline for non-CF bronchiectasis.Thorax. 2010 Jul;65Suppl 1:i1-58.http://www.ncbi.nlm.nih.gov/pubmed/20627931

[xxii] Ceftriaxone, IV: Pasteur MC, Bilton D, Hill AT; British Thoracic Society Bronchiectasis non-CF Guideline Group. British Thoracic Society guideline for non-CF bronchiectasis.Thorax. 2010 Jul;65Suppl 1:i1-58.http://www.ncbi.nlm.nih.gov/pubmed/20627931

[xxiii] Amoxicillin/clavulanic acid: Pasteur MC, Bilton D, Hill AT; British Thoracic Society Bronchiectasis non-CF Guideline Group. British Thoracic Society guideline for non-CF bronchiectasis.Thorax. 2010 Jul;65Suppl 1:i1-58.http://www.ncbi.nlm.nih.gov/pubmed/20627931

Amoxicllin/clavulanic acid: NICD pneumococci susceptibility data for amoxicillin for the period 2005-2014 [E-mail communication]

Amoxicillin/clavulanic acid:Kiffer CR, Pignatari AC. Pharmacodynamic evaluation of commonly prescribed oral antibiotics against respiratory bacterial pathogens. BMC Infect Dis. 2011 Oct 25;11:286.http://www.ncbi.nlm.nih.gov/pubmed/22026724

[xxv] Grading of COPD: Global Initiative for Chronic Obstructive Lung Disease 2023 Report: GOLD Executive Summary. Eur Respir J. 2023 Apr 1;61(4):2300239. doi: 10.1183/13993003.00239-2023.

[xxvi] Modified MRC dyspnea scale: Vogelmeier CF, Criner GJ, Martinez FJ, Anzueto A, Barnes PJ, Bourbeau J, Celli BR, Chen R, Decramer M, Fabbri LM, Frith P, Halpin DM, López Varela MV, Nishimura M, Roche N, Rodriguez-Roisin R, Sin DD, Singh D, Stockley R, Vestbo J, Wedzicha JA, Agustí A. Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Lung Disease 2017 Report. GOLD Executive Summary. Am J Respir Crit Care Med. 2017 Mar 1;195(5):557-582. https://www.ncbi.nlm.nih.gov/pubmed/28128970

Modified MRC dyspnea scale: Williams N. The MRC breathlessness scale. Occup Med (Lond). 2017 Aug 1;67(6):496-497 https://www.ncbi.nlm.nih.gov/pubmed/28898975

[xxvii]Prednisone: Leuppi JD., Schuetz P., Bingisser R., Bodmer M., Briel M., Drescher T., Duerring U., Henzen C., Leibbrandt Y., Maier S., Miedinger D., Muller B., Scherr A., Schindler C., Stoeckli R., Viatte S., von Garnier C., Tamm J. 2013. Short-term vs Conventional Glucocorticoid Therapy in Acute Exacerbations of Chronic Obstructive Pulmonary Disease. The REDUCE Randomized Clinical Trial. JAMA. Vol 309(21): 2223-2231 http://www.ncbi.nlm.nih.gov/pubmed/23695200

[xxviii]Prednisone: Leuppi JD., Schuetz P., Bingisser R., Bodmer M., Briel M., Drescher T., Duerring U., Henzen C., Leibbrandt Y., Maier S., Miedinger D., Muller B., Scherr A., Schindler C., Stoeckli R., Viatte S., von Garnier C., Tamm J. 2013. Short-term vs Conventional Glucocorticoid Therapy in Acute Exacerbations of Chronic Obstructive Pulmonary Disease. The REDUCE Randomized Clinical Trial. JAMA. Vol 309(21): 2223-2231 http://www.ncbi.nlm.nih.gov/pubmed/23695200

[xxix] Antibiotics – acute exacerbations: Global Initiative for Chronic Obstructive Lung Disease (GOLD 2023) page 142-143 https://www.sciencedirect.com/science/article/pii/S2590143520300038

[xxx]Amoxicillin/clavulanic acid: GERMSA 2015 susceptibility data. www.nicd.ac.za

Amoxicillin/clavulanic acid, oral:Vollenweider DJ, Jarrett H, Steurer-Stey CA, Garcia-Aymerich J, Puhan MA. Antibiotics for exacerbations of chronic obstructive pulmonary disease. Cochrane Database Syst Rev. 2012 Dec 12;12:CD010257.http://www.ncbi.nlm.nih.gov/pubmed/23235687

[xxxi]Moxifloxacin: NICD susceptibility data. [E-mail communication]

[xxxii]LAMA + LABA combination preferred. and also: COPD chronic GRADE B: Global Initiative for Chronic Obstructive Lung Disease (GOLD 2023), page 118, https://www.sciencedirect.com/science/article/pii/S2590143520300038 https://respiratory-research.biomedcentral.com/articles/10.1186/s12931-021-01648-5 https://erj.ersjournals.com/content/42/6/1484

[xxxiii]Formoterol inhaler:Nannini LJ, Lasserson TJ, Poole P. Combined corticosteroid and long-acting beta(2)-agonist in one inhaler versus long-acting beta(2)-agonists for chronic obstructive pulmonary disease. Cochrane Database Syst Rev. 2012 Sep12;9:CD006829.http://www.ncbi.nlm.nih.gov/pubmed/22972099

[xxxiv]Formoterol inhaler:Nannini LJ, Lasserson TJ, Poole P. Combined corticosteroid and long-acting beta(2)-agonist in one inhaler versus long-acting beta(2)-agonists for chronic obstructive pulmonary disease. Cochrane Database Syst Rev. 2012 Sep12;9:CD006829.http://www.ncbi.nlm.nih.gov/pubmed/22972099

[xxxv]Long-acting β2-agonist/corticosteroid combination inhaler:eLong-acting β2-agonist/corticosteroid combination inhaler:Kew KM, Dias S, Cates CJ. Long-acting inhaled therapy (beta-agonists,anticholinergics and steroids) for COPD: a network meta-analysis. CochraneDatabase Syst Rev. 2014 Mar 26;3:CD010844.http://www.ncbi.nlm.nih.gov/pubmed/24671923

[xxxvi] Inhaled corticosteroids (Patients on protease inhibitors): Kedem E, Shahar E, Hassoun G, Pollack S. Iatrogenic Cushing's syndrome due to coadministration of ritonavir and inhaled budesonide in an asthmatic human immunodeficiency virus infected patient. J Asthma. 2010 Sep;47(7):830-1. https://www.ncbi.nlm.nih.gov/pubmed/20653496

Inhaled corticosteroids (Patients on protease inhibitors): Frankel JK, Packer CD. Cushing's syndrome due to antiretroviral-budesonide interaction. Ann Pharmacother. 2011 Jun;45(6):823-4. https://www.ncbi.nlm.nih.gov/pubmed/21558486

Inhaled corticosteroids (Patients on protease inhibitors): Blondin MC, Beauregard H, Serri O. Iatrogenic Cushing syndrome in patients receiving inhaled budesonide and itraconazole or ritonavir: two cases and literature review. Endocr Pract. 2013 Nov-Dec;19(6):e138-41. https://www.ncbi.nlm.nih.gov/pubmed/23807527

Inhaled corticosteroids (Patients on protease inhibitors): Yoganathan K, David L, Williams C, Jones K. Cushing's syndrome with adrenal suppression induced by inhaled budesonide due to a ritonavir drug interaction in a woman with HIV infection. Int J STD AIDS. 2012 Jul;23(7):520-1. https://www.ncbi.nlm.nih.gov/pubmed/22844010

[xxxvii] Theophylline:Ford PA, Durham AL, Russell RE, Gordon F, Adcock IM, Barnes PJ. Treatment effects of low-dose theophylline combined with an inhaled corticosteroid in COPD. Chest. 2010 Jun;137(6):1338-44. doi: 10.1378/chest.09-2363. Epub 2010 Mar 18. http://www.ncbi.nlm.nih.gov/pubmed/20299628

Theophylline: Cosio BG, Iglesias A, Rios A, Noguera A, Sala E, Ito K, Barnes PJ, Agusti A. Low-dose theophylline enhances the anti-inflammatory effects of steroids during exacerbations of COPD. Thorax. 2009 May;64(5):424-9. http://www.ncbi.nlm.nih.gov/pubmed/19158122

[xxxviii]Moxifloxacin: Ott SR, Allewelt M, Lorenz J, Reimnitz P, Lode H; German Lung Abscess Study Group. Moxifloxacin vs ampicillin/sulbactam in aspiration pneumonia and primary lung abscess.Infection. 2008 Feb;36(1):23-30. http://www.ncbi.nlm.nih.gov/pubmed/18231720

[xxxix] Chest x-ray diagnosis (diagnosis of community acquired pneumonia): Boyles TH, Brink A, Calligaro GL, Cohen C, Dheda K, Maartens G, et al; South African Thoracic Society; Federation of Infectious Diseases Societies of Southern Africa. South African guideline for the management of community-acquired pneumonia in adults. J Thorac Dis. 2017 Jun;9(6):1469-1502. https://www.ncbi.nlm.nih.gov/pubmed/28740661

[xl] Chest x-ray diagnosis (follow-up for community acquired pneumonia): Tang KL, Eurich DT,Minhas-Sandhu JK,Marrie TJ,Majumdar SR. Incidence, correlates, and chest radiographic yield of new lung cancer diagnosis in 3398 patients with pneumonia. Arch Intern Med 2011;171:1193–1198. https://www.ncbi.nlm.nih.gov/pubmed/21518934

Chest x-ray diagnosis (follow-up for community acquired pneumonia): Mortensen EM, Copeland LA, Pugh MJ, Fine MJ, Nakashima B, Restrepo MI, de Molina RM, Anzueto A. Diagnosis of pulmonary malignancy after hospitalization for pneumonia. Am J Med. 2010 Jan;123(1):66-71. https://www.ncbi.nlm.nih.gov/pubmed/20102994

Chest x-ray diagnosis (follow-up for community acquired pneumonia): Metlay JP, Waterer GW, Long AC, Anzueto A, Brozek J, Crothers K, et al. Diagnosis and Treatment of Adults with Community-acquired Pneumonia. An Official Clinical Practice Guideline of the American Thoracic Society and Infectious Diseases Society of America. Am J Respir Crit Care Med. 2019 Oct 1;200(7):e45-e67. https://www.ncbi.nlm.nih.gov/pubmed/31573350

Chest x-ray diagnosis (follow-up for community acquired pneumonia): Lim WS, Baudouin SV, George RC, Hill AT, Jamieson C, Le Jeune I, Macfarlane JT, Read RC, Roberts HJ, Levy ML, Wani M, Woodhead MA; Pneumonia Guidelines Committee of the BTS Standards of Care Committee. BTS guidelines for the management of community acquired pneumonia in adults: update 2009. Thorax. 2009 Oct;64 Suppl 3:iii1-55. https://www.ncbi.nlm.nih.gov/pubmed/19783532

Chest x-ray diagnosis (follow-up for community acquired pneumonia):

[xli]Oxygen: Chu DK, Kim LH, Young PJ, Zamiri N, Almenawer SA, Jaeschke R, Szczeklik W, Schünemann HJ, Neary JD, Alhazzani W. Mortality and morbidity in acutely ill adults treated with liberal versus conservative oxygen therapy (IOTA): a systematic review and meta-analysis. Lancet. 2018 Apr 28;391(10131):1693-1705. https://www.ncbi.nlm.nih.gov/pubmed/29726345

[xlii]Duration of antibiotic therapy (community acquired pneumonia): Tansarli GS, Mylonakis E. Systematic Review and Meta-analysis of the Efficacy of Short-Course Antibiotic Treatments for Community-Acquired Pneumonia in Adults.Antimicrob Agents Chemother. 2018 Aug 27;62(9). pii: e00635-18. https://www.ncbi.nlm.nih.gov/pubmed/29987137

Duration of antibiotic therapy (community acquired pneumonia): Boyles TH, Brink A, Calligaro GL, Cohen C, Dheda K, Maartens G, et al; South African Thoracic Society; Federation of Infectious Diseases Societies of Southern Africa. South African guideline for the management of community-acquired pneumonia in adults. J Thorac Dis. 2017 Jun;9(6):1469-1502. https://www.ncbi.nlm.nih.gov/pubmed/28740661

Duration of antibiotic therapy (community acquired pneumonia): Metlay JP, Waterer GW, Long AC, Anzueto A, Brozek J, Crothers K, et al. Diagnosis and Treatment of Adults with Community-acquired Pneumonia. An Official Clinical Practice Guideline of the American Thoracic Society and Infectious Diseases Society of America. Am J Respir Crit Care Med. 2019 Oct 1;200(7):e45-e67. https://www.ncbi.nlm.nih.gov/pubmed/31573350

[xliii] Criteria for de-escalation of IV antibiotic therapy (community acquired pneumonia): Oosterheert JJ, Bonten MJ, Schneider MM, Buskens E, Lammers JW, Hustinx WM, Kramer MH, Prins JM, Slee PH, Kaasjager K, Hoepelman AI. Effectiveness of early switch from intravenous to oral antibiotics in severe community acquired pneumonia: multicentre randomised trial. BMJ. 2006 Dec 9;333(7580):1193. https://www.ncbi.nlm.nih.gov/pubmed/17090560

Criteria for de-escalation of IV antibiotic therapy (community acquired pneumonia): Mertz D, Koller M, Haller P, Lampert ML, Plagge H, Hug B, Koch G, Battegay M, Flückiger U, Bassetti S. Outcomes of early switching from intravenous to oral antibiotics on medical wards. J Antimicrob Chemother. 2009 Jul;64(1):188-99. https://www.ncbi.nlm.nih.gov/pubmed/19401304

Criteria for de-escalation of IV antibiotic therapy (community acquired pneumonia): Boyles TH, Brink A, Calligaro GL, Cohen C, Dheda K, Maartens G, et al; South African Thoracic Society; Federation of Infectious Diseases Societies of Southern Africa. South African guideline for the management of community-acquired pneumonia in adults. J Thorac Dis. 2017 Jun;9(6):1469-1502. https://www.ncbi.nlm.nih.gov/pubmed/28740661

Criteria for de-escalation of IV antibiotic therapy (community acquired pneumonia): Nathwani D, Lawson W, Dryden M, Stephens J, Corman S, Solem C, Li J, Charbonneau C, Baillon-Plot N, Haider S, Eckmann C. Implementing criteria-based early switch/early discharge programmes: a European perspective. Clin Microbiol Infect. 2015 Sep;21 Suppl 2:S47-55. https://www.ncbi.nlm.nih.gov/pubmed/26198369

[xliv]Ceftriaxone: Carratalà J, Garcia-Vidal C, Ortega L, Fernández-Sabé N, Clemente M, Albero G, López M, Castellsagué X, Dorca J, Verdaguer R, Martínez-Montauti J, Manresa F, Gudiol F. Effect of a 3-step critical pathway to reduce duration of intravenous antibiotic therapy and length of stay in community-acquired pneumonia: a randomized controlled trial. Arch Intern Med. 2012 Jun 25;172(12):922-8. http://www.ncbi.nlm.nih.gov/pubmed/22732747

Ceftriaxone: Oosterheert JJ, Bonten MJ, Schneider MM, Buskens E, Lammers JW, Hustinx WM, Kramer MH, Prins JM, Slee PH, Kaasjager K, Hoepelman AI. Effectiveness of early switch from intravenous to oral antibiotics in severe community acquired pneumonia: multicentre randomised trial. BMJ. 2006 Dec 9;333(7580):1193. http://www.ncbi.nlm.nih.gov/pubmed/17090560

Ceftriaxone, IV: Pasteur MC, Bilton D, Hill AT; British Thoracic Society Bronchiectasis non-CF Guideline Group. British Thoracic Society guideline for non-CF bronchiectasis. Thorax. 2010 Jul;65 Suppl 1:i1-58.http://www.ncbi.nlm.nih.gov/pubmed/20627931

Ceftriaxone, IV: Perry TR, Schentag JJ. Clinical use of ceftriaxone: a pharmacokinetic-pharmacodynamic perspective on the impact of minimum inhibitory concentration and serum protein binding. *Clin Pharmacokinet.* 2001;40(9):685-94. http://www.ncbi.nlm.nih.gov/pubmed/11605716

Ceftriaxone, IV: NICD pneumococci susceptibility data for amoxicillin for the period 2005-2014 [E-mail communication]

[xiv]Amoxicillin/clavulanic acid: Pasteur MC, Bilton D, Hill AT; British Thoracic Society Bronchiectasis non-CF Guideline Group. British Thoracic Society guideline for non-CF bronchiectasis.Thorax. 2010 Jul;65Suppl 1:i1-58.http://www.ncbi.nlm.nih.gov/pubmed/20627931

Amoxicllin/clavulanic acid: NICD pneumococci susceptibility data for amoxicillin for the period 2005-2014 [E-mail communication]

Amoxicillin/clavulanic acid: Kiffer CR, Pignatari AC. Pharmacodynamic evaluation of commonly prescribed oral antibiotics against respiratory bacterial pathogens. BMC Infect Dis. 2011 Oct 25;11:286. http://www.ncbi.nlm.nih.gov/pubmed/22026724

Amoxicillin/clavulanic acid: Allegra L, Blasi F, de Bernardi B, Cosentini R, Tarsia P. Antibiotic treatment and baseline severity of disease in acute exacerbations of chronic bronchitis: a re-evaluation of previously published data of a placebo-controlled randomized study. Pulm Pharmacol Ther. 2001;14(2):149-55. http://www.ncbi.nlm.nih.gov/pubmed/11273797

Amoxicillin/clavulanic acid, oral: Vollenweider DJ, Jarrett H, Steurer-Stey CA, Garcia-Aymerich J, Puhan MA. Antibiotics for exacerbations of chronic obstructive pulmonary disease. Cochrane Database Syst Rev. 2012 Dec 12;12:CD010257. http://www.ncbi.nlm.nih.gov/pubmed/23235687

[xlvii]Azithromycin, oral: Zervos M, Martinez FJ, Amsden GW, Rothermel CD, Treadway G. Efficacy and safety of 3-day azithromycin versus 5-day moxifloxacin for the treatment of acute bacterial exacerbations of chronic bronchitis. Int J Antimicrob Agents. 2007 Jan;29(1):56-61. http://www.ncbi.nlm.nih.gov/pubmed/17189096

Azithromycin, oral: Amsden GW, Baird IM, Simon S, Treadway G. Efficacy and safety of azithromycin vs levofloxacin in the outpatient treatment of acute bacterial exacerbations of chronic bronchitis. Chest. 2003 Mar;123(3):772-7. http://www.ncbi.nlm.nih.gov/pubmed/12628877

Azithromycin, IV: South African Medicines Formulary. 12th Edition. Division of Clinical Pharmacology. University of Cape Town. 2016.

[xlviii]Moxifloxacin: Sun T, Sun L, Wang R, Ren X, Sui DJ, Pu C, Ren Y, Liu Y, Yang Z, Li F. Clinical efficacy and safety of moxifloxacin versus levofloxacin plus metronidazole for community-acquired pneumonia with aspiration factors. Chin Med J (Engl). 2014;127(7):1201-5. http://www.ncbi.nlm.nih.gov/pubmed/24709166

Moxifloxacin: Ott SR, Allewelt M, Lorenz J, Reimnitz P, Lode H; German Lung Abscess Study Group. Moxifloxacin vs ampicillin/sulbactam in aspiration pneumonia and primary lung abscess.Infection. 2008 Feb;36(1):23-30. http://www.ncbi.nlm.nih.gov/pubmed/18231720

[xlix] Sputum induction with nebulised sodium chloride: Antel K, Oosthuizen J, Malherbe F, Louw VJ, Nicol MP, Maartens G, Verburgh E. Diagnostic accuracy of the Xpert MTB/Rif Ultra for tuberculosis adenitis. BMC Infect Dis. 2020 Jan 13;20(1):33. https://www.ncbi.nlm.nih.gov/pubmed/31931736

[l] LAM urine testing (DS-TB): NDoH. Guidance on the use of Lateral flow urine lipoarabinomannan essay for the diagnosis of active tuberculosis in people living with HIV. Feb 2021 https://knowledgehub.health.gov.za/system/files/elibdownloads/2023-04/TB%2520LAM%2520Guidelines%2520-%252008%2520Feb%25202021%2520%25282%2529.pdf

LAM urine testing (DS-TB): Bjerrum S, Schiller I, Dendukuri N, Kohli M, Nathavitharana RR, Zwerling AA, Denkinger CM, Steingart KR, Shah M. Lateral flow urine lipoarabinomannan assay for detecting active tuberculosis in people living with HIV. Cochrane Database Syst Rev. 2019 Oct 21;10:CD011420. https://www.ncbi.nlm.nih.gov/pubmed/31633805

[li] BPaL-M regimen: NDoH. Review - Adolopment_WHO_DRTB_Guidelines_4May2023_Final

CHAPTER 17

EAR, NOSE AND THROAT DISORDERS

17.1 EPIGLOTTITIS

J05.1

DESCRIPTION

Acute epiglottitis can result in severe, sudden or progressive airway obstruction.
Acute epiglottitis can be caused by bacteria (e.g. *H. influenzae*), viruses (e.g. herpes simplex) and non-infectious insults (trauma, chemicals, heat).

GENERAL MEASURES

Airway management may require urgent specialist advice.
Adequate hydration.

MEDICINE TREATMENT

Humidified oxygen.

Antibiotic therapy
Total duration of therapy: 10 days.

- Ceftriaxone, IV, 1 g daily.

Follow with oral therapy as soon as patient can swallow and the temperature is <37.8°C for 24 hours, to complete the 10-day course:

- Amoxicillin/clavulanic acid, oral, 875/125 mg 12 hourly.

Severe penicillin allergy to amoxicillin/clavulanic acid, oral: (Z88.0)

- Macrolide, e.g.:
- Azithromycin, oral, 500mg daily for 3 days.

LoE:III[i]

Acute stage
Imminent airway obstruction:

- Hydrocortisone, IV, 100 mg immediately as a single dose.

AND *LoE:III*[ii]

- Adrenaline (epinephrine) 1:1 000, 1 mL nebulised.
  - Dilute to 5 mL with sodium chloride 0.9% and administer 4–6 hourly.

LoE:III[iii]

17.2 RHINITIS, ALLERGIC, PERSISTENT

J30.1-4

DESCRIPTION

Allergic rhinitis is an allergic inflammation of the nasal airways. Signs and symptoms include rhinorrhoea, itching, sneezing, nasal congestion and obstruction, conjunctival swelling and erythema, puffy eyes, swollen nasal turbinates, and middle ear effusion.

GENERAL MEASURES

Avoid allergens and irritants.
Provide education on the correct technique of administering topical medicines. Incorrect technique is a common cause of treatment failure.

MEDICINE TREATMENT

- Corticosteroid, topical, nasal spray e.g.:
- Fluticasone topical, aqueous nasal spray, 1 spray of 100 mcg in each nostril daily.
  - Aim the nozzle laterally and upwards (aim for the eye) and not to the back of the throat.
  - Do not sniff vigorously.

LoE:I[iv]

Patients on protease inhibitors:

- Beclomethasone, aqueous nasal solution, 1 spray of 100 mcg in each nostril 12 hourly.
  - Aim the nozzle laterally and upwards (aim for the eye) and not to the back of the throat.
  - Do not sniff vigorously.
  - Review 3 monthly.

LoE:II[v]

If symptoms persist despite an adequate trial of topical corticosteroids administered with the correct technique:

ADD

- Non-sedating antihistamine, oral e.g.:
- Cetirizine, oral, 10 mg daily.

LoE:I[vi]

For relief of nasal blockage**:**

- Oxymetazoline 0.05%, intranasal, administered 8 hourly for a maximum of 5 days.

Note: Rebound nasal congestion occurs with prolonged use (>5 days) of topical nasal decongestants.

LoE:III[vii]

Failure of the above:

ADD

- Corticosteroids (intermediate-acting) e.g.:
- Prednisone, oral, 30 mg daily for 5 days whilst continuing the topical steroid.

17.3 SINUSITIS, BACTERIAL, COMPLICATED

J01.0-4/J01.8-9

DESCRIPTION

Acute bacterial sinusitis complicated by extension to the orbit or intracranially.
Extension to the orbit causes orbital cellulitis or orbital periosteal abscess, both of which may present with pain on eye movement, partial or complete visual loss

(which can be irreversible), ophthalmoplegia, and proptosis. Eyelid oedema and erythema is usually present, but external signs of inflammation may be absent. Intracranial extension may cause meningitis, subdural empyema, brain abscess, or thrombosis of cavernous sinus/cortical veins.

In immunosuppressed or diabetic patients presenting with features of sinusitis consider fungal infections such as mucormycosis. Features suggesting mucormycosis include necrosis of the nasal or palatal mucosa, and orbital or cerebral involvement.

MEDICINE TREATMENT

- Ceftriaxone, IV, 2 g 12 hourly and **refer**.

Pain:

- Paracetamol, oral, 500 mg to 1 g, 4 to 6 hourly as required (to a maximum of 4 g in 24 hours).
  - Maximum dose: 15 mg/kg/dose.

LoE:III

REFERRAL

Urgent

» Proptosis.
» Ophthalmoplegia.
» Suspected mucormycosis, especially in immunocompromised patients.

Non-urgent

» After initiating antimicrobial therapy, refer for a CT scan, to a centre where an appropriate surgical specialist, i.e. ophthalmologist, ENT specialist or neurosurgeon, is available.
» Suspected fungal sinusitis (other than mucormycosis).

17.4 OTITIS MEDIA, ACUTE

H66.9

DESCRIPTION

Inflammation of the middle ear of rapid onset.

MEDICINE TREATMENT

In previously untreated patients:

- Amoxicillin, oral, 1000 mg 8 hourly for 5 days.

LoE:III[viii]

Patients not responding to amoxicillin:

- Amoxicillin/clavulanic acid, oral, 875/125 mg 12 hourly for 5 days.

LoE:III[ix]

Severe penicillin allergy: (Z88.0)

- Macrolide, e.g.:
- Azithromycin, oral, 500 mg daily for 3 days.

For patients with upper respiratory tract congestion, secondary to allergy: (T78.4)
- Non-sedating antihistamine, oral, e.g.:
- Cetirizine, oral, 10 mg daily for 10 days. *LoE:II*[x]

For management of allergic rhinitis, see Section 17.2: Rhinitis, allergic, persistent.

For pain:
- Paracetamol, oral, 500 mg to 1 g, 4 to 6 hourly as required (to a maximum of 4 g in 24 hours).
  - Maximum dose: 15 mg/kg/dose.

If pain is not controlled, see chapter 26: Pain. *LoE:III*[xi]

REFERRAL
» No response to amoxicillin/clavulanic acid.
» No pain relief despite treatment.
» Bulging eardrum, not responding to treatment after 24 hours.
» Swelling and pain on palpation of the mastoid process.
» Recurrent otitis media.

17.5 OTITIS MEDIA, CHRONIC, SUPPURATIVE
H66.1-3

DESCRIPTION
A purulent discharge from the ear for more than 2 weeks.
If the eardrum has been ruptured for 2 weeks or longer, a secondary infection with multiple organisms usually occurs. Multiple organism infection often makes oral antibiotic treatment ineffective and patients may need to be referred.
TB is an important cause of a chronically discharging ear in South Africa.
If pain is present, suspect another condition or complications.
Note:
» A chronically draining ear can only heal if it is dry.
» Drying the ear is time consuming but is the most effective treatment.
» HIV status should be established in chronic otitis media.

GENERAL MEASURES
Dry mopping is the most important part of the treatment. It should be demonstrated to the patient.
» Roll a piece of clean absorbent cloth into a wick.
» Carefully insert the wick into the ear with twisting action.
» Remove the wick and replace with a clean dry wick.
» Repeat this until the wick is dry when removed.

Do not leave anything in the ear.
Avoid getting the inside of the ear wet while swimming and bathing.
Exclude TB as a cause.

MEDICINE TREATMENT

After cleaning and drying the ear:

- Acetic acid 2% in alcohol, topical, 3–4 drops instilled into the ear every 6 hours for 5 days.
- Ciprofloxacin, drops, 3 mg/mL, 3–4 drops instilled into the ear every 8 hours for 7 days after mopping.

LoE:I[xii]

For pain:

- Paracetamol, oral, 500 mg to 1 g, 4 to 6 hourly as required (to a maximum of 4 g in 24 hours).
  - Maximum dose: 15 mg/kg/dose.

If pain is not controlled, see chapter 26: Pain. LoE:III[xiii]

REFERRAL

» Focal neurological signs such as facial nerve palsy.
» Vomiting or drowsiness.
» Swelling and pain on palpation of the mastoid process.
» No improvement after 4 weeks.
» Any attic perforation.
» Any perforation not progressively improving after 3 months or closed by 6 months, even if dry.
» Moderate or severe hearing loss.
» Effusion.

17.6 MASTOIDITIS

H70.0/H70.9

DESCRIPTION

Infection of the mastoid air cells, usually complicating otitis media. Most patients have tenderness, erythema, and/or swelling over the mastoid bone. Diagnosis should be confirmed radiographically, preferably by CT scan.

MEDICINE TREATMENT

- Ceftriaxone, IV, 2 g 12 hourly.

REFERRAL

After initiating antimicrobial therapy, refer to a centre for s mastoidectomy.

17.7 OTITIS EXTERNA

17.7.1 OTITIS EXTERNA, NECROTISING

H60.2

DESCRIPTION

Invasive infection of the external auditory canal, which can extend to involve the base of the skull with cranial nerve palsies and the temporomandibular joint. Presents with severe otalgia and otorrhoea, which is unresponsive to topical therapy for otitis externa. Most common pathogen: *P. aeruginosa*.

Necrotising otitis externa typically occurs in elderly diabetics or other immunocompromised patients.

GENERAL MEASURES

Debridement as indicated.
Insert a dry wick such as a dried sponge, into the canal under direct vision. Remove the wick 2 days later, and replace if necessary.

MEDICINE TREATMENT

- Ciprofloxacin, oral, 750 mg 12 hourly, and refer. *LoE:III*

REFERRAL

» For surgical debridement of necrotic bone in non-responders.
» All cases to a centre where CT scan of the affected area can be done to assess the extent of the disease.
» Cranial nerve palsies.

17.8 ABSCESS, PERITONSILLAR

J36

DESCRIPTION

Peritonsillar abscess or quinsy is a collection of pus lateral to the tonsil, i.e. underneath it pushing it toward the midline. Infections are often polymicrobial. It typically presents with trismus and sore throat. Other features include:

» unilateral throat pain
» dysphagia
» drooling
» muffled voice
» fever

SURGICAL MEASURES

Drainage of pus is the most important intervention.
There are 3 main methods:

» needle aspiration of pus
» incision and drainage
» abscess tonsillectomy, either unilateral or bilateral.

MEDICINE TREATMENT

Antibiotic therapy

Total duration of therapy: 10 days.

- Amoxicillin/clavulanic acid, IV, 1.2 g 8 hourly.

Follow with oral therapy as soon as patient can swallow and the temperature is <37.8ºC for 24 hours:

- Amoxicillin/clavulanic acid, oral, 875/125 mg 12 hourly.

Severe penicillin allergy: (Z88.0)

- Clindamycin, IV, 600 mg 8 hourly.

Follow with oral therapy as soon as patient can swallow and the temperature is <37.8ºC for 24 hours:

- Clindamycin, oral, 450 mg 8 hourly.

For pain:

- NSAID, oral: e.g.
- Ibuprofen, oral, 400 mg 8 hourly with or after a meal.

REFERRAL

Refer all for ENT and/or anaesthetic review.

Urgent

» Signs of airway compromise (e.g. stridor)).
» Suspicion of infective spread beyond the peritonsillar space.

17.9 VERTIGO, ACUTE

R42/H81.1

DESCRIPTION

An acute syndrome, consisting of vertigo, nystagmus, nausea, vomiting and postural instability. It is important to differentiate between peripheral and central causes of vestibular dysfunction.

Peripheral causes

Patients frequently present with vertigo, which is most often rotational, with nystagmus. The onset is usually sudden and often intermittent. Associated abnormalities of hearing may be present. Aetiology includes benign paroxysmal positional vertigo (confirm with a positive Dix-Hallpike test, https://www.youtube.com/watch?v=8RYB2QIO1N4), aminoglycoside vestibular toxicity, and vestibular neuritis.

Central causes

It is essential to conduct a thorough neurological examination in patients with vertigo, looking specifically for signs of brainstem or cerebellar dysfunction.

Aetiology includes cerebellar stroke and space occupying lesions of the posterior cranial fossa.

GENERAL MEASURES

It is essential to find the cause and treat appropriately. Patients with suspected central causes should be referred for neuro-imaging and possible neurosurgical management.

Benign positional vertigo

H81.1

Good results may be achieved with particle relocation manoeuvres, such as the Epley manoeuvre. https://www.youtube.com/watch?v=jBzID5nVQjk

In a third of patients, symptoms recur after 1 year and repeat manoeuvres may be required.

MEDICINE TREATMENT

This is only for symptomatic relief and is determined by the aetiology.

Discontinue all medication as soon as symptoms subside as the medicine itself may cause vertigo due to involvement of the unaffected side.

- Promethazine, oral, 10 mg 8 hourly.
  - May be increased to 20 mg 8 hourly if necessary.

Note: This is sedating and patients should not drive or operate heavy machinery.

LoE:I[xiv]

REFERRAL

» If there is no peripheral cause, suspect intracranial mass lesions or cerebellar stroke.
» Patients not responding to therapy for exclusion of alternative aetiology.

References:

[i] Azithromycin, oral: Wasserman S, Boyles T, Mendelson M. South African antibiotic stewardship programme (SAASP): A pocket guide to antibiotic prescribing for adults in South Africa, 2015. http://www.fidssa.co.za/images/SAASP_Antibiotic_Gudidelines_2015.pdf

[ii] Hydrocortisone, IV::Riffat F, Jefferson N, Bari N, McGuinness J. Acute supraglottitis in adults. Ann OtolRhinolLaryngol. 2011 May;120(5):296-9. http://www.ncbi.nlm.nih.gov/pubmed/21675584

Hydrocortisone, IV: Mayo-Smith MF, Spinale JW, Donskey CJ, Yukawa M, Li RH, Schiffmann FJ. Acute epiglottitis: an 18-year old experience in Rhode Island. Chest 1995;108:1640–7. http://www.ncbi.nlm.nih.gov/pubmed/7497775

Hydrocortisone, IV: Bizaki AJ, Numminen J, Vasama JP, Laranne J, Rautiainen M. Acute supraglottitis in adults in Finland: review and analysis of 308 cases. Laryngoscope. 2011 Oct;121(10):2107-13. http://www.ncbi.nlm.nih.gov/pubmed/21898436

Hydrocortisone, IV: Wick R, Ballmer PE, Haller A. Acute epiglottitis in adults. Swiss Med Wkly 2002; 132: 541–7. http://www.ncbi.nlm.nih.gov/pubmed/12557859

Hydrocortisone, IV: Hafidh MA, Sheahan P, Keogh I, Walsh RM. Acute epiglottitis in adults: a recent experience with 10 cases. J Laryngol Otol. 2006 Apr;120(4):310-3. http://www.ncbi.nlm.nih.gov/pubmed/16623975

[iii] Adrenaline (epinephrine), nebulisation: Wick R, Ballmer PE, Haller A. Acute epiglottitis in adults. Swiss Med Wkly 2002; 132: 541–7. http://www.ncbi.nlm.nih.gov/pubmed/12557859

[iv] Corticosteroids, topical nasal (therapeutic class): Chong LY, Head K, Hopkins C, Philpott C, Burton MJ, Schilder AG. Different types of intranasal steroids for chronic rhinosinusitis. Cochrane Database Syst Rev. 2016 Apr 26;4:CD011993. https://www.ncbi.nlm.nih.gov/pubmed/27115215

Corticosteroids, topical nasal (therapeutic class): South African Medicines Formulary. 12th Edition. Division of Clinical Pharmacology. University of Cape Town. 2016.

Corticosteroids, topical nasal (therapeutic class): Herman H. Once-daily administration of intranasal corticosteroids for allergic rhinitis: a comparative review of efficacy, safety, patient preference, and cost. Am J Rhinol. 2007 Jan-Feb;21(1):70-9. https://www.ncbi.nlm.nih.gov/pubmed/17283565

Fluticasone, topical, aqueous nasal spray: Contract circular HP07-2017DAI.

[v] Beclomethasone, topical, aqueous nasal spray (drug-drug interaction with protease inhibitors): Foisy MM, Yakiwchuk EM, Chiu I, Singh AE. Adrenal suppression and Cushing's syndrome secondary to an interaction between ritonavir and fluticasone: a review of the literature. HIV Med. 2008 Jul;9(6):389-96. https://www.ncbi.nlm.nih.gov/pubmed/18459946

Beclomethasone, topical, aqueous nasal spray (drug-drug interaction with protease inhibitors): University of Liverpool. HIV drug interaction database. https://www.hiv-druginteractions.org/

Beclomethasone, topical, aqueous nasal spray (drug-drug interaction with protease inhibitors): Frankel JK, Packer CD. Cushing's syndrome due to antiretroviral-budesonide interaction. Ann Pharmacother. 2011 Jun;45(6):823-4. https://www.ncbi.nlm.nih.gov/pubmed/21558486

Beclomethasone, topical, aqueous nasal spray (drug-drug interaction with protease inhibitors): Yoganathan K, David L, Williams C, Jones K. Cushing's syndrome with adrenal suppression induced by inhaled budesonide due to a ritonavir drug interaction in a woman with HIV infection. Int J STD AIDS. 2012 Jul;23(7):520-1. https://www.ncbi.nlm.nih.gov/pubmed/22844010

[vi] Non-sedating antihistamines, oral: Howarth PH, Stern MA, Roi L, Reynolds R, Bousquet J. Double-blind, placebo-controlled study comparing the efficacy and safety of fexofenadine hydrochloride (120 and 180 mg once daily) and cetirizine in seasonal allergic rhinitis. J Allergy ClinImmunol. 1999;104(5):927-933. https://www.ncbi.nlm.nih.gov/pubmed/10550734

Non-sedating antihistamines, oral: Olasińska-Wiśniewska A , Olasiński J, Grajek S. Cardiovascular safety of antihistamines. Postep Derm Alergol. 2014, 3: 182–186. https://www.ncbi.nlm.nih.gov/pubmed/25097491

Non-sedating antihistamines, oral: National Department of Health: Affordable Medicines, EDP-Adult Hospital level. Medicine Review: Non-sedating antihistamines for persistent allergic rhinitis, 23 November 2017. http://www.health.gov.za/

Cetirizine, oral: Contract circular HP 09-2016SD.

[vii] Oxymetazoline intranasal: South African Medicines Formulary. 12th Edition. Division of Clinical Pharmacology. University of Cape Town. 2016.

[viii] Amoxicillin, oral (acute otitis media): Brink AJ, Cotton M, Feldman C, Finlayson H, Friedman R, Green R, Hendson W, Hockman M, Maartens G, Madhi S, Reubenson G, Silverbauer E, Zietsman I. Updated recommendations for the management of upper respiratory tract infections in South Africa. S Afr Med J. 2015 Apr 6;105(5):344-52. https://www.ncbi.nlm.nih.gov/pubmed/26242659

[ix] Azithromycin, oral: Contract circular RT301-2017

[x] Antihistamines, oral (Cetirizine): Griffin G, Flynn CA. Antihistamines and/or decongestants for otitis media with effusion (OME) in children. Cochrane Database Syst Rev. 2011 Sep 7;(9):CD003423. https://www.ncbi.nlm.nih.gov/pubmed/21901683

[xi] Paracetamol, oral: Sjoukes A, Venekamp RP, van de Pol AC, Hay AD, Little P, Schilder AG, Damoiseaux RA. Paracetamol (acetaminophen) or non-steroidal anti-inflammatory drugs, alone or combined, for pain relief in acute otitis media in children. Cochrane Database Syst Rev. 2016 Dec 15;12:CD011534. https://www.ncbi.nlm.nih.gov/pubmed/27977844

Paracetamol, oral: National Department of Health, Essential Drugs Programme: Primary Health Care STGs and EML, 2018. http://www.health.gov.za/

[xii] Ciprofloxain, topical: Onali MA, Bareeqa SB, Zia S, Ahmed SI, Owais A, Ahmad AN. Efficacy of Empirical Therapy With Combined Ciprofloxacin Versus Topical Drops Alone in Patients With Tubotympanic Chronic Suppurative Otitis Media: A Randomized Double-Blind Controlled Trial. Clin Med Insights Ear Nose Throat. 2018 Jan 11;11:1179550617751907. https://www.ncbi.nlm.nih.gov/pubmed/29348711

[xiii] Paracetamol, oral: National Department of Health, Essential Drugs Programme: Primary Health Care STGs and EML, 2018. http://www.health.gov.za/

[xiv] Promethazine, oral: James AL, Burton MJ. Betahistine for Menière's disease or syndrome. Cochrane Database Syst Rev. 2001;(1):CD001873.http://www.ncbi.nlm.nih.gov/pubmed/11279734

CHAPTER 18

EYE DISORDERS

For many eye conditions early specialist consultation and advice is required. To mitigate delays in referral it is recommended that electronic consultation methods are utilised with transmission of appropriate images so that appropriate treatment can be initiated before referral.

18.1 CONJUNCTIVITIS

H10.9

DESCRIPTION

Inflammation of the conjunctiva, usually due to allergy or infection (viral or bacterial).
Conjunctivitis is usually bilateral. Other causes of a red eye are often unilateral.
The condition is self-limiting and usually resolves within 14 days.

GENERAL MEASURES

If it is due to an infection, counsel on the importance of:

» frequent hand washing,
» using separate linen, towels and washcloths, and
» avoiding direct contact with infected material or individuals.

Contact lenses should not be worn if conjunctivitis is present or during a course of topical therapy. Soft lenses should not be worn within 24 hours of instilling eye drops containing the preservative benzalkonium chloride.

18.1.1 CONJUNCTIVITIS, VIRAL

B30.1+ (H13.1*)

DESCRIPTION

Viral conjunctivitis is the commonest cause of infective conjunctivitis. It may be unilateral but often progresses to bilateral. Adenovirus is the commonest viral conjunctivitis, however other viral causes of conjunctivitis present in the same way.

Clinical features:

» Viral conjunctivitis may be associated with an upper respiratory tract infection.
» A burning, sandy, or gritty feeling in the eyes.
» Morning crusting followed by watery discharge.
» Preauricular lymphadenopathy may be present.
» The cornea, iris, and pupil are completely normal with normal visual acuity.

The condition is self-limiting, but eye irritation and discharge may get worse for the first week depending on the specific virus. Duration varies from 3-5 days to 2-3 weeks before resolution.

MEDICINE TREATMENT

- Sodium chloride 0.9%, eye washes or irrigation.

If sodium chloride 0.9% is not available, use cooled boiled water/sterile water.

- Oxymetazoline 0.025%, ophthalmic drops, instil 1 drop 6 hourly for a maximum of 7 days to reduce redness of eyes.

18.1.2 CONJUNCTIVITIS, ALLERGIC

See Primary Health Care Standard Treatment Guidelines and Essential Medicine List; Section 18.1.1 Conjunctivitis, allergic.

18.1.3 CONJUNCTIVITIS, BACTERIAL (NON-GONOCOCCAL)

H10.0

DESCRIPTION

Clinical features:

» It may be either unilateral or bilateral.
» There is matting of lashes in the morning with the eyelids stuck shut.
» There is a mucopurulent discharge throughout the day.
» The eyelids may be swollen.

MEDICINE TREATMENT

- Immediate irrigation of the eyes with sodium chloride 0.9%.

During the day:

- Chloramphenicol 1%, ophthalmic ointment 6 hourly for 7 days.

LoE: IVb[i]

OR

- Fluoroquinolone ophthalmic drops as second-line treatment (i.e. poor response to chloramphenicol or contra-indication/drug interactions with chloramphenicol) e.g.:
- Ciprofloxacin 0.3%, ophthalmic drops, instil 1 drop 2 hourly for 2 days.
  - Then reduce frequency to 1 drop 4 hourly during waking hours, for 5 days.

LoE: IIb[ii]

REFERRAL

No response to treatment.

18.1.4 CONJUNCTIVITIS, BACTERIAL (GONOCOCCAL)

H10.0

Hyperacute bacterial conjunctivitis involves rapid onset and progression of conjunctivitis and is often caused by *N. gonorrhoeae*. **Gonococcal conjunctivitis requires immediate referral to an ophthalmologist to prevent corneal involvement and potential perforation.**

Clinical features:

» Hyperpurulent discharge.
» Diminished visual acuity.
» Eye tenderness.
» Swollen lymph nodes.

For conjunctivitis of the newborn, See Primary Health Care Standard Treatment Guidelines and Essential Medicine List; Section 18.1.3.

MEDICINE TREATMENT

- Ceftriaxone, IM, 250 mg as a single dose. W
  - For ceftriaxone IM injection: Dissolve ceftriaxone 250 mg in 0.9 mL lidocaine 1% without epinephrine (adrenaline).

AND

- Azithromycin, oral, 1 g as a single dose. W

For persistent infection, refer to Section 25.1 Male urethral syndrome or Section 25.2 Vaginal discharge syndrome.

REFERRAL

Refer all cases to an ophthalmologist immediately.

18.2 ENDOPHTHALMITIS, BACTERIAL

S05.4-6 + (Y43.99), H44.0

DESCRIPTION

Infection of the ocular cavity is an emergency as it can cause blindness. This may occur secondary to bacteraemia (endogenous infection) or, more commonly, after penetrating ocular injury or surgery.
In patients with endogenous endophthalmitis blood cultures should be done and the source of infection identified and treated.
In patients with endophthalmitis after penetrating injury/surgery culture should be done on specimens of aqueous or vitreous humour.

MEDICINE TREATMENT

Refer immediately to an ophthalmologist.

Endogenous endophthalmitis
Specialist initiated; vitrectomy often required:

- Ceftriaxone, IV, 2 g daily for 7 days. W

Adjust antibiotics according to culture and sensitivity results.
AND

- Ceftazidime, intravitreal, 2.25 mg. W

LoE:IIIb[iii]

AND

- Vancomycin, intravitreal, 1 mg. W
  - Administer antibiotics using separate tuberculin syringes.
  - Antibiotic doses may be repeated after 48 hours depending on culture results or clinical response.

LoE:IIIb[iv]

LoE:IIIb[v]

Post-surgical endophthalmitis
Specialist initiated; vitrectomy often required:

- Ceftazidime, intravitreal, 2.25 mg. W

AND

- Vancomycin, intravitreal, 1 mg. W
  - Administer antibiotics using separate tuberculin syringes.
  - Antibiotic doses may be repeated after 48 hours depending on culture results or clinical response.

LoE:IIIb[vi]

In addition, if there is soft tissue involvement or as prophylaxis after a penetrating eye injury:

- Ciprofloxacin, oral, 750 mg 12 hourly for 7 days. W

18.3 GLAUCOMA
H40.0-6/H40.8-9

DESCRIPTION
Glaucoma is characterised by damage to the optic nerve with associated visual field loss, for which raised intra-ocular pressure (IOP) is a primary risk factor. Glaucoma is classified as open-angle or angle-closure. Glaucoma may occur as a primary condition or secondary to other ocular conditions. The condition is usually bilateral but may be unilateral or asymmetrical (especially with secondary causes).

18.3.1 OPEN-ANGLE GLAUCOMA
H40.1

DESCRIPTION
» Mostly asymptomatic.
» History of gradual loss of vision in the affected eye or loss of visual field.

» Often suspected after seeing cupping of optic disc on routine fundoscopy or finding elevated intra-ocular pressure on screening.

MEDICINE TREATMENT

Refer to an ophthalmology unit for diagnosis and initiation of treatment.

First line

ß-blocker monotherapy:

- Non-selective β-blocker, e.g.: *LoE:IIb[vii]*
- Timolol 0.25%, ophthalmic drops, instil 1 drop 12 hourly.

OR

Selective β-blocker: *LoE:IVb*

- Betaxolol 0.25–0.5%, ophthalmic drops, instil 1 drop 12 hourly.

Second line *LoE:IIb[viii]*

- Prostaglandin analogue monotherapy, e.g.:
  - Latanoprost 0.005%, ophthalmic drops, instil 1 drop daily.
  - Use as first line if patient has contra-indication to ß-blocker.
  - Use in place of ß-blocker if patient has intolerable side effects with ß-blocker or if there is no significant reduction in IOP with ß-blocker.

OR

- Prostaglandin analogue in combination with non-selective ß-blocker if there is insufficient reduction in IOP with ß-blocker monotherapy, e.g.
  - Bimatoprost 0.03% + Timolol 0.5% *LoE:Ib[ix]*

OR

- Prostaglandin analogue in combination with selective ß-blocker if there a contraindication to a non-selective ß-blocker e.g.
  - Latanoprost 0,005% with betaxolol 0.25-0.5%

Third line

Intolerance to prostaglandin analogue, or poor response:

- Alpha-agonist, e.g.: *LoE:IIIb[x]*
  - Brimonidine 0.15–0.2%, ophthalmic drops, instil 1 drop 12 hourly.
  - Use as second line if patient is allergic to prostaglandin analogue.
  - Use in place of prostaglandin analogue if there is no significant further reduction in IOP when adding prostaglandin analogue to ß-blocker.
  - Use in combination with ß-blocker and prostaglandin analogue if the patient still has progression of disease or target IOP is not reached.

Failure to respond: *LoE:IVb*

Alternatives in consultation with a specialist:

Parasympathomimetic agent:

- Pilocarpine 1%, ophthalmic drops, instil 1 drop 6 hourly.

In severe cases, as a temporary measure before ocular surgery, in consultation with a specialist: *LoE:IIIb*[xi]

Carbonic anhydrase inhibitor:

- Acetazolamide, oral, 250 mg 6 hourly.

REFERRAL

All to an ophthalmology unit.

18.3.2 ACUTE ANGLE-CLOSURE GLAUCOMA

H40.2

DESCRIPTION

» Usually presents acutely with sudden onset of severe eye pain and redness, associated with nausea, vomiting and hemicranial headache.
» Loss of vision in the affected eye.
» Coloured haloes or bright rings around lights.
» Hazy-looking cornea.
» Fixed, semi-dilated pupil.
» Shallow anterior chamber.
» Severely elevated intra-ocular pressure. When measured with finger palpation, the affected eye feels hard, compared to the other eye.
» If intraocular pressure rises more slowly, the patients may be asymptomatic with gradual loss of vision.

MEDICINE TREATMENT

Institute initial therapy and then refer IMMEDIATELY to an ophthalmology unit.

Try to achieve immediate reduction in IOP:

- Acetazolamide, oral, 500 mg immediately as a single dose.
  - Followed by 250 mg 6 hourly.

AND

- Timolol 0.25–0.5%, ophthalmic drops, instil 1 drop 12 hourly.

Also treat patient for associated pain and nausea. See Sections 12.4.1: Perioperative analgesics and 12.6.5.2: Treatment of PONV.

Where those measures fail, for short-term use only:

- Mannitol, IV, 1.5–2 g/kg as a 20% solution over 30–60 minutes.

OR

Glycerol, oral, 1 g/kg of 50% solution as a single dose immediately.

REFERRAL

All to an ophthalmology unit.

18.4 HERPES ZOSTER OPHTHALMICUS

B02.3, G53.0

DESCRIPTION

Herpes zoster ophthalmicus (HZO) occurs when the varicella-zoster virus reactivates in the trigeminal ganglion and passes down the ophthalmic division of the trigeminal nerve. Patients present with a painful vesicular rash in the trigeminal V1 area – vesicles on the tip of the nose indicate nasociliary branch involvement, which indicates the risk of ocular involvement. A minority of patients may develop conjunctivitis, keratitis, uveitis, retinitis, and cranial nerve involvement (oculomotor or optic nerves). Permanent sequelae of ophthalmic zoster infection may include chronic ocular inflammation, loss of vision, and debilitating post-herpetic neuralgia. All patients should be offered HIV testing.

MEDICINE TREATMENT

- Aciclovir, oral, 800 mg 5 doses per day (4 hourly while awake) for 7–10 days.
    - Treatment should be initiated within the first three days of onset of symptoms, except in HIV-infected patients who should be treated if there are active skin lesions. *LoE:IVb*

For patients unable to take oral medication, severely immunocompromised patients and for patients with complicated HZO e.g. acute retinal necrosis (ARN), optic neuropathy or orbitopathy:

- Aciclovir, IV infusion over one hour, 10 mg/kg 8 hourly for 7-14 days.
    - Seek specialist advice for duration of treatment and for switching to oral aciclovir therapy.
    - Adjust dose based on renal clearance (See Appendix II for guidance on prescribing and monitoring). *LoE:IIIb*[xii]

Post-herpetic neuralgia:

Initiate treatment with adjuvant therapy (i.e. amitriptyline) early.
See Section 25.1.4: Neuropathic pain (Post-herpetic neuralgia).

LoE:IIIb[xiii]

REFERRAL

» Vesicles on the tip of the nose.
» Fluorescein staining of cornea shows corneal/ulceration.
» Decreased vision.
» Red eye (uveitis or keratitis).
» Cranial nerve palsies.

18.5 KERATITIS

18.5.1 KERATITIS, HERPES SIMPLEX

B00.5† + (H19.1*)

DESCRIPTION

Acute unilateral painful red eye with visual blurring and decreased corneal sensation. Characteristic dendritic corneal ulcer seen on staining with fluorescein.

MEDICINE TREATMENT

- Aciclovir, oral, 400 mg five times daily for 10–14 days. *LoE:Ib[xiv]*

Note: Topical corticosteroids are contraindicated for treating dendritic ulcers.

18.5.2 KERATITIS, SUPPURATIVE

H16.8

DESCRIPTION

Painful red eye with corneal lesion that stains with fluorescein and has creamy white appearance. Contact lenses are a major risk factor, especially for bacterial infections. Have a high index of suspicion for fungal infection in PLHIV, or there is a history of injury to eye with plant matter.

MEDICINE TREATMENT

Empiric therapy until culture results become available:

Bacterial infection:

- Fluoroquinolone ophthalmic drops, e.g.:
- Ciprofloxacin 0.3%, ophthalmic drops, instil 1 drop hourly for 3 days.
  - Then reduce frequency to 1 drop 3–4 hourly until the ulcer is completely healed.
  - Patients requiring treatment for longer than 2 weeks should be on the advice of an ophthalmologist.

LoE: IVb[xv]

Fungal infection:

- Natamycin 5%, ophthalmic drops, instil 1 drop 1–2 hourly for 3–4 days. (Specialist prescribed).
  - Then reduce frequency to 1 drop 3–4 hourly.
  - Continue for 14–21 days until resolution of infection.

LoE: Ib[xvi]

REFERRAL

» All patients to be managed in consultation with an ophthalmologist.

18.6 RETINITIS, HIV CMV

H30.9 + (B20.2)

DESCRIPTION

Cytomegalovirus (CMV) retinitis is seen in advanced HIV infection, with CD4 count <100 cells/mm^3. The characteristic retinal appearance is that of necrosis, i.e. white exudates, and hemorrhages at the edges of the exudates. Visual loss is irreversible – the goal of therapy is to limit further loss.

MEDICINE TREATMENT

Limited CMV retinitis:

- Valganciclovir, oral, 900 mg 12 hourly for the first 3 weeks, then 900 mg daily until immune recovery (CD4 >100) and a minimum of 3 months of therapy with valganciclovir (if available). *LoE:IIIb*[xvii]
  - Monitor FBC weekly during induction, then monthly, as valganciclovir can cause bone marrow suppression. Avoid concomitant zidovudine use.
  - Initiate ART 2 weeks after starting induction therapy.

If valganciclovir is not available:

- Ganciclovir, intravitreal, 2 mg twice a week for three weeks then once a week (specialist).
  - Once immune function has been restored with antiretroviral therapy (CD4 >100) and the features of active retinitis has cleared, maintenance ganciclovir can be stopped but monitor for recurrence.

REFERRAL

To ophthalmologist for confirmation of diagnosis.
Patients with extensive or wide-spread CMV infection to be managed by an infectious disease specialist.

18.7 UVEITIS

H20.0

Uveitis can be associated with systemic diseases or infection, necessitating a careful history and review of presenting symptoms. Physical examination of the eye and pertinent organ systems should be performed to characterise the type of inflammation present and any concomitant systemic disease. Multimodal ophthalmic imaging has an important role in characterising certain types of intraocular inflammation. Determining the specific type of uveitis guides the selection of treatment. The goal of treatment is to control the disease activity and eliminate or reduce the risk of loss of vision. Uveitis is often classified anatomically based on the primary site of inflammation: anterior uveitis (iris and ciliary body), intermediate uveitis (vitreous), posterior uveitis (retina or choroid) and panuveitis (whole eye), with posterior segments of the eye generally associated with more severe disease.

18.7.1 INFECTIOUS UVEITIS

H20.0

Infectious uveitis may be caused by:

» Bacteria - (syphilis (refer to Section 6.8 syphilis, Section 14.6.3 meningovascular syphilis), tuberculosis (refer to Section 16.9 pulmonary TB, Section 16.10 Pleural TB), bartonellosis).
» Viruses - (herpes (refer to Section 4.11.2 Herpes zoster, Section 14.6.2 Herpes simplex encephalitis, Section 18.4 Herpes Zoster ophthalmicus, Section 18.5 Herpes simplex keratitis, Section 25.3 recurrent herpes simplex), cytomegalovirus (refer to Section 10.2.6 CMV, Section 18.6 retinitis, HIV CMV).
» Fungi - (histoplasmosis).
» Protozoa - (toxoplasmosis (refer to Section 10.2.10 Cerebral toxoplasmosis), toxocariasis, and cysticercosis (refer to Section 14.6.6 neurocysticercosis)).

Patients must be investigated for infectious causes. Further screening should be performed which should be informed by obtaining a full clinical history along with presenting signs and symptoms. Consider the following for further investigation:

» TB - Chest XR or TB.
» Syphilis – VDRL test.
» Toxoplasmosis - toxoplasma PCR.
» Herpes simplex and Herpes zoster: HSV or HZV PCR.
» Cat-scratch disease (bartonella): bartonella PCR.

If an infectious cause is found, treatment of the ocular disease is as for the systemic disease. Once the infection has been addressed, residual inflammation can be treated with adjuvant anti-inflammatory therapy.

18.7.2 NON-INFECTIOUS UVEITIS, ANTERIOR

H20.0

DESCRIPTION

The commonest form of non-infectious uveitis is acute anterior uveitis, which presents with pain and photophobia, variable loss of vision, circumcilliary injection, and a miotic pupil. Chronic anterior uveitis may lead to cystoid macular oedema with decreased central acuity, cataract formation, and secondary glaucoma.

MEDICINE TREATMENT

- Cycloplegic agent, e.g.:
- Atropine 1%, ophthalmic drops, instil 1 drop 12 hourly.

AND

- Corticosteroids, e.g.:
- Dexamethasone 0.1%, ophthalmic drops, instil 1–2 drops 4–6 hourly.

LoE:Ib[xviii]

REFERRAL

All, for management at an ophthalmology unit.

18.7.3 NON-INFECTIOUS POSTERIOR UVEITIS AND PANUVEITIS

H20.0

DESCRIPTION

Non-infectious posterior and panuveitis may be sight limiting if inflammation is not controlled. Both auto-inflammatory and autoimmune processes may be implicated. Posterior uveitis and panuvetis both present similarly with loss of vision, pain and photophobia, floaters and a red eye and are treated similarly as outlined below.

Indicators of severe inflammation include:

» Impairment of visual function.
» Bilateral disease.
» Vitreous haze.
» Macular or optic nerve disease.
» Retinal vascular inflammation.
» Exudative detachment.
» Ocular structural complications that threaten visual function.

LoE:IVb[xix]

MEDICINE TREATMENT

- Cycloplegic agent, e.g.:
- Atropine 1%, ophthalmic drops, instil 1 drop 12 hourly.

- Corticosteroids, e.g.:

<u>Acute inflammation/flare</u>

- Prednisone, oral 1 mg/kg/day (max 80 mg/day) for one week
  - Use lowest possible dose for shortest possible duration to control inflammation.
  - Apply a dose tapering regimen over 3-6 weeks typically reducing doses every 1-2 days based on treatment response.

LoE:IIb[xx]

<u>Chronic inflammation</u>

- Prednisone, oral 1 mg/kg/day (max 80 mg/day) for no longer than one month.
  - Use lowest possible dose for shortest possible duration to control inflammation.

- Apply a dose tapering regimen typically reducing doses every 1-2 weeks based on treatment response.
- Monitor for infection, hypertension, fluid retention, diabetes mellitus, hyperlipidaemia, atherosclerosis, osteoporosis, glaucoma, and cataracts.

Patients requiring corticosteroid-sparing control or for persistent severe inflammation refractory to corticosteroid therapy:

Initiation of immunosuppressant therapy should be considered under the following conditions: *LoE:IVb*[xxi]

» Worsening of disease while on high dose corticosteroids
» No response to high dose corticosteroids after 2 to 4 weeks
» Lack of control of inflammation following treatment with high dose corticosteroids for 4 weeks.
» Patients requiring maintenance corticosteroid doses ≥7.5 mg/day for three or more consecutive months.
» Contra-indication or intolerance to corticosteroids. *LoE:IVb*[xxii]

- DMARDs (Disease-modifying antirheumatic drugs).
- Methotrexate, oral, 7.5 mg once weekly. *LoE:IIb*[xxiii]
  - Dose titration should be based on individual patient response using increments of 2.5 mg weekly to a maximum dose of 25 mg weekly.
  - As the onset of action is slow with a delayed time to full effect, commence dose tapering of concomitant corticosteroid therapy 2 weeks after initiating methotrexate therapy, based on treatment response.
  - Pre-treatment screening: exclude any infectious diseases that may be exacerbated by immunosuppression.
  - Monitoring: FBC and LFTs at baseline, 4 weeks after initiating treatment and 8 weekly thereafter.
  - Methotrexate is teratogenic - ensure women of child-bearing potential are counselled.

AND

- Folic acid, oral 5 mg daily

Patients presenting with concomitant anterior uveitis should also be managed with topical treatment (see Section 18.7.1: Infectious uveitis).

REFERRAL

All, for management at an ophthalmology unit.
If there is concomitant systemic disease refer to appropriate specialist.

18.8 SURGICAL AND DIAGNOSTIC PRODUCTS

Ocular peri-operative pharmaceutical products

- Sodium hyaluronate 10 mg/mL.
- Acetylcholine chloride (for intra-ocular irrigation).
- Sterile intraocular irrigating solution.
- Hyaluronidase 1500 IU injection (adjunct to anaesthesia for cataract surgery). *LoE:IIb*[xxiv]
- Mitomycin C 2 mg injection (for sponge application during trabeculectomy for glaucoma management). *LoE:IIb*[xxv]

Ocular diagnostic products

- Fluorescein 2%, ophthalmic drops.
- Fluorescein ophthalmic strips.
- Tropicamide 1%, ophthalmic drops.
- Cyclopentolate 2 mg/mL ophthalmic drops (for cycloplegic refraction).
- Cyclopentolate 2 mg/mL and phenylephrine 10 mg/mL (for fundoscopic examination).
- Polyacrylic acid 2 mg/g ophthalmic gel (as coupling liquid for diagnostic contact lenses).

▪ **Local anesthetics used on the eye**

- Oxybuprocaine hydrochloride 0.4%. *LoE:IIIb*[xxvi]

▪ **Preparations for tear deficiency**

- Hydroxypropyl methylcellulose 0.3–0.5%.

18.9 DRY EYE DISEASE

H04.1

DESCRIPTION

Dry eye occurs when there is inadequate tear volume or function. It is a multifactorial disease of the ocular surface.

The common symptoms include feelings of dryness, grittiness, burning and foreign body sensation, usually worse during the day. A stringy discharge, redness and transient blurring of vision are also common.
Allergic conjunctivitis should be excluded.

GENERAL MEASURES

The management of dry eye involves controlling the symptoms, since the disease is generally not curable.
Management encompasses both pharmacologic and non-pharmacologic approaches.

Relieve symptoms with warm compresses, i.e. a clean moistened cloth over the eyes for at least 1 minute two to three times per day.
Patients should be educated to avoid over the counter topical medications, many of which exacerbate dryness, and control their environmental factors (e.g. encourage frequent blinking during visually attentive tasks, avoid air conditioners or heating, use humidifiers).

MEDICINE TREATMENT

Tear substitutes:

- Hydroxypropyl methylcellulose, ophthalmic drops, 1 drop, 6 hourly.

OR *LoE:IVb*[xxvii]

Lanolin, anhydrous liquid, ophthalmic ointment, at night.

LoE:IVb[xxviii]

18.10 MEDICAL MANAGEMENT OF EYE INJURY

18.10.1 CHEMICAL BURN

This is a medical emergency.
See Primary Health Care Standard Treatment Guidelines Section 18.3.1: Eye injury, chemical burn.

18.10.2 EYE INJURY: BLUNT/PENETRATING/ FOREIGN BODY

See Primary Health Care Standard Treatment Guidelines Sections 18.3.2 Eye injury/foreign bodies and 18.3.3: Eye injury (blunt or penetrating).

References:

[i] Chloramphenicol 1%, ophthalmic ointment: South African Medicines Formulary. 12th Edition. Division of Clinical Pharmacology. University of Cape Town, 2016.

[ii] Fluoroquinolone ophthalmic drops: Sheikh A, Hurwitz B, van Schayck CP, McLean S, Nurmatov U. Antibiotics versus placebo for acute bacterial conjunctivitis. Cochrane Database Syst Rev. 2012 Sep 12;(9):CD001211. https://www.ncbi.nlm.nih.gov/pubmed/22972049

Fluoroquinolone ophthalmic drops: Epling J. Bacterial conjunctivitis. BMJ Clin Evid. 2012 Feb 20;2012. pii: 0704. https://www.ncbi.nlm.nih.gov/pubmed/22348418

Fluoroquinolone ophthalmic drops: Silver LH, Woodside AM, Montgomery DB. Clinical safety of moxifloxacin ophthalmic solution 0.5% (VIGAMOX) in pediatric and nonpediatric patients with bacterial conjunctivitis. Surv Ophthalmol. 2005 Nov;50 Suppl 1:S55-63. https://www.ncbi.nlm.nih.gov/pubmed/16257311

Fluoroquinolone ophthalmic drops (ciprofloxacin ophthalmic drops - dosing): South African Medicines Formulary. 12th Edition. Division of Clinical Pharmacology. University of Cape Town, 2016.

Fluoroquinolone ophthalmic drops (ciprofloxacin ophthalmic drops - dosing): Leibowitz HM. Antibacterial effectiveness of ciprofloxacin 0.3% ophthalmic solution in the treatment of bacterial conjunctivitis. Am J Ophthalmol. 1991 Oct;112(4 Suppl):29S-33S. https://www.ncbi.nlm.nih.gov/pubmed/1928271

[iii] Ceftazidime, intravitreal: Yonekawa Y, Chan RV, Reddy AK, Pieroni CG, Lee TC, Lee S. Early intravitreal treatment of endogenous bacterial endophthalmitis. Clin Experiment Ophthalmol.2011 Nov;39(8):771-8. http://www.ncbi.nlm.nih.gov/pubmed/22050564

Ceftazidime, intravitreal: Okada AA, John RP, Liles WC, D'Amico DJ, Baker AS. Endogenous bacterial endophthalmitis. Report of a ten-year retrospective study 1994;101(5):832-838. http://www.ncbi.nlm.nih.gov/pubmed/8190467

[iv] Vancomycin, intravitreal: Yonekawa Y, Chan RV, Reddy AK, Pieroni CG, Lee TC, Lee S. Early intravitreal treatment of endogenous bacterial endophthalmitis. Clin Experiment Ophthalmol.2011 Nov;39(8):771-8. http://www.ncbi.nlm.nih.gov/pubmed/22050564

Vancomycin, intravitreal: Okada AA, Johnson RP, Liles WC, D'Amico DJ, Baker AS. Endogenous bacterial endophthalmitis. Report of a ten-year retrospective study. Ophthalmology. 1994 May;101(5):832-8. http://www.ncbi.nlm.nih.gov/pubmed/8190467

[v] Intravitreal antibiotics (repeat doses): Durand ML.Endophthalmitis. Clinical Microbiology and Infection 2013;19(3):227-34. As cited in Cochrane review Emami S, Kitayama K, Coleman AL. Adjunctive steroid therapy versus antibiotics alone for acute endophthalmitis a#er intraocular procedure. Cochrane Database of Systematic Reviews 2022, Issue 6. Art. No.: CD012131. DOI: 10.1002/14651858.CD012131.pub3.

[vi] Intravitreal antibiotics (repeat doses): Durand ML.Endophthalmitis. Clinical Microbiology and Infection 2013;19(3):227-34. As cited in Cochrane review Emami S, Kitayama K, Coleman AL. Adjunctive steroid therapy versus antibiotics alone for acute endophthalmitis a#er intraocular procedure. Cochrane Database of Systematic Reviews 2022, Issue 6. Art. No.: CD012131. DOI: 10.1002/14651858.CD012131.pub3.

[vii] Non-selective β-blocker, ophthalmic drops: Geyer O, Lazar M, Novack GD, Shen D, Eto CY. Levobunolol compared with timolol: a four-year study. Br J Ophthalmol. 1988 Dec;72(12):892-6. http://www.ncbi.nlm.nih.gov/pubmed/3067745

Non-selective β-blocker, ophthalmic drops: Mills KB, Wright G. A blind randomised cross-over trial comparing metipranolol 0.3% with timolol 0.25% in open-angle glaucoma: a pilot study. Br J Ophthalmol. 1986 Jan;70(1):39-42.http://www.ncbi.nlm.nih.gov/pubmed/2868753

[viii] Prostaglandin analogues, ophthalmic drops: Parrish RK, Palmberg P, Sheu WP; XLT Study Group. A comparison of latanoprost, bimatoprost, and travoprost in patients with elevated intraocular pressure: a 12-week, randomized, masked-evaluator multicenter study. Am J Ophthalmol. 2003 May;135(5):688-703.http://www.ncbi.nlm.nih.gov/pubmed/12719078

[ix] Bimatoprost 0.01%, ophthalmic drops: National Department of Health: Affordable Medicines, EDP-Adult Hospital level. Evidence summary: Bimatoprost 0.01% vs 0.03% for glaucoma, August 2019. http://www.health.gov.za/

Bimatoprost 0.01%, ophthalmic drops: Katz LJ, Cohen JS, Batoosingh AL, Felix C, Shu V, Schiffman RM. Twelve-month, randomized, controlled trial of bimatoprost 0.01%, 0.0125%, and 0.03% in patients with glaucoma or ocular hypertension. Am J Ophthalmol. 2010 Apr;149(4):661-671.e1. https://www.ncbi.nlm.nih.gov/pubmed/20346780

[x]Alpha-agonist, ophthalmic drops: Schadlu R, Maus TL, Nau CB, Brubaker RF. Comparison of the efficacy of apraclonidine and brimonidine as aqueous suppressants in humans. Arch Ophthalmol. 1998 Nov;116(11):1441-4. http://www.ncbi.nlm.nih.gov/pubmed/9823343

Alpha-agonist, ophthalmic drops: South African Medicines Formulary. 12th Edition. Division of Clinical Pharmacology. University of Cape Town, 2016.

[xi]Acetazolamide, oral: Maus TL, Larsson LI, McLaren JW, Brubaker RF. Comparison of dorzolamide and acetazolamide as suppressors of aqueous humor flow in humans. Arch Ophthalmol. 1997 Jan;115(1):45-9. http://www.ncbi.nlm.nih.gov/pubmed/9006424

[xii] Aciclovir, IV: Sellitti TP et al. (1993). Association of Herpes Zoster Ophthalmicus With Acquired Immunodeficiency Syndrome and Acute Retinal Necrosis. AMERICAN JOURNAL OF OPHTHALMOLOGY.
Werner RN et al. (2016). A. European consensus-based (S2k) Guideline on the Management of Herpes Zoster - guided by the European Dermatology Forum (EDF) in cooperation with the European Academy of Dermatology and Venereology (EADV), Part 2: Treatment. J Eur Acad Dermatol Venereol.

[xiii] Amitriptyline, oral: Bowsher D. The effects of pre-emptive treatment of postherpetic neuralgia with amitriptyline: a randomized, double-blind, placebo-controlled trial. J Pain Symptom Manage. 1997 Jun;13(6):327-31.http://www.ncbi.nlm.nih.gov/pubmed/9204652

[xiv] Aciclovir, oral: Wilhelmus KR. Antiviral treatment and other therapeutic interventions for herpes simplex virus epithelial keratitis. Cochrane Database Syst Rev. 2015 Jan 9;1:CD002898. https://www.ncbi.nlm.nih.gov/pubmed/25879115

[xv] Fluoroquinolone ophthalmic drops: Lin A, Rhee MK, Akpek EK, Amescua G, Farid M, Garcia-Ferrer FJ, Varu DM, Musch DC, Dunn SP, Mah FS; American Academy of Ophthalmology Preferred Practice Pattern Cornea and External Disease Panel. Bacterial Keratitis Preferred Practice Pattern®. Ophthalmology. 2019 Jan;126(1):P1-P55. https://www.ncbi.nlm.nih.gov/pubmed/30366799

[xvi] Natamycin: FlorCruz NV, Evans JR. Medical interventions for fungal keratitis. Cochrane Database Syst Rev. 2015 Apr 9;(4):CD004241. doi: 10.1002/14651858.CD004241.pub4. PMID: 25855311.

[xvii] Valganciclovir, oral: Roche Products (Pty) Ltd. Valcyte 450 film coated tablet®, South African package insert, 27 July 2012.

Valganciclovir, oral: Martin DF, Sierra-Madero J, Walmsley S, Wolitz RA, Macey K, Georgiou P, Robinson CA, Stempien MJ; Valganciclovir Study Group. A controlled trial of valganciclovir as induction therapy for cytomegalovirus retinitis. N Engl J Med. 2002 Apr 11;346(15):1119-26. Erratum in: N Engl J Med 2002 Sep 12;347(11):862. http://www.ncbi.nlm.nih.gov/pubmed/11948271

Valganciclovir, oral (3 months duration): Centers for Disease Control and Prevention. Guidelines for prevention and treatment of opportunistic infections in HIV-Infected adults and adolescents recommendations from CDC, the National Institutes of Health, and the HIV Medicine Association of the Infectious Diseases Society of America. MMWR 2009;58(RR-4):1-216. http://www.cdc.gov/mmwr/pdf/rr/rr5804.pdf

[xviii] Corticosteroids, ophthalmic drops (therapeutic class): McGhee CN, Dean S, Danesh-Meyer H. Locally administered ocular corticosteroids: benefits and risks. Drug Saf. 2002;25(1):33-55. http://www.ncbi.nlm.nih.gov/pubmed/11820911

Corticosteroids, ophthalmic drops: National Department of Health: Affordable Medicines, EDP-Adult Hospital level. Medicine Review: Prednisiolone 1% vs Dexamethsone 0.01% ophthalmic drops for uveitis, May 2018. http://www.health.gov.za/

Corticosteroids, ophthalmic drops: Espinosa G, Muñoz-Fernández S, García Ruiz de Morales JM, Herreras JM, Cordero-Coma M. Treatment recommendations for non-infectious anterior uveitis. Med Clin (Barc). 2017 Dec 20;149(12):552.e1-552.e12. https://www.ncbi.nlm.nih.gov/pubmed/28911893

[xix] Dick AD et al. (2018). American Academy of Ophthalmology. Guidance on Noncorticosteroid Systemic. American Academy of Ophthalmology, 757-773.

[xx] NDoH Review. Evidence review of the use of prednisone/prednisolone for severe bilateral posterior and panuveitis. 9 February 2023

Jabs D et al. Guidelines for the Use of Immunosuppressive Drugs in Patients With Ocular Inflammatory Disorders: Recommendations of an Expert Panel AMERICAN JOURNAL OF OPHTHALMOLOGY OCTOBER 2000

[xxi] Jabs D et al. Guidelines for the Use of Immunosuppressive Drugs in Patients With Ocular Inflammatory Disorders: Recommendations of an Expert Panel AMERICAN JOURNAL OF OPHTHALMOLOGY OCTOBER 2000

[xxii] Wakefield et al pre-treatment assessment Review panel. Inflammatory eye disease: Pre-treatment assessment of patients prior to commencing immunosuppressive and biologic therapy: Recommendations from an expert committee. Autoimmun Rev. 2017 Mar;16(3):213-222. doi: 10.1016/j.autrev.2017.01.003. Epub 2017 Jan 27. PMID: 28137477.

[xxiii] NDoH Review. Corticosteroid-sparing agents for severe uveitis. July 2023

[xxiv] NDoH Evidence review. Hyaluronidase for cataract surgery. 9 February 2023

[xxv] NDoH Evidence review. Intraoperative MMC or 5-FU during trabeculectomy for glaucoma management. 30 November 2023

[xxvi] Local anaesthetics, ophthalmic drops: Lawrenson JG, Edgar DF, Tanna GK, Gudgeon AC. Comparison of the tolerability and efficacy of unit-dose, preservative-free topical ocular anaesthetics. Ophthalmic Physiol Opt. 1998 Sep;18(5):393-400. https://www.ncbi.nlm.nih.gov/pubmed/10023471

[xxvii] Hydroxypropylmethylcellulose, ophthalmic drops: South African Medicines Formulary. 12th Edition. Division of Clinical Pharmacology. University of Cape Town, 2016.

[xxviii] Lanolin, anhydrous liquid, ophthalmic ointment: South African Medicines Formulary. 12th Edition. Division of Clinical Pharmacology. University of Cape Town, 2016.

CHAPTER 19
POISONING

POISONS INFORMATION CENTRES

Poisons Information Helpline (national service)	24/7	0861 555 777
Red Cross War Memorial Children's Hospital Poisons Information Centre Email: poisonsinformation@uct.ac.za http://www.paediatrics.uct.ac.za/poisons-information-centre		
Tygerberg Poisons Information Centre Email: toxicology@sun.ac.za www.sun.ac.za/poisoncentre		
University of the Free State Poison Control and Medicine Information Centre	24/7	082 491 0160
Telephone numbers tested June 2025		

Access poisons information at: https://www.afritox.co.za/
The Afritox database is available free of charge to public hospitals in South Africa. If the above centres cannot be contacted, enquire at the nearest trauma and emergency unit.

ENVENOMATION

Envenomation is an instance of poisoning by venom resulting from a bite or sting from an animal such as a snake, spider, scorpion, insect, or marine life.

South African Vaccine Producers (SAVP): For procurement of Snake/spider/scorpion antivenom: Email: benita.mouton@nhls.ac.za	Office hours: (011) 386 6062/6063/6078 After hours 071 680 9897

19.1 INSECT BITES AND STINGS

T63.4 + (X23.99/X24.99/X25.99/X29.99)

DESCRIPTION

Toxicity due to insect bites and stings usually results in local effects only and systemic effects are rare. Occasionally, hypersensitivity reactions are encountered, varying from minor local inflammation to acute anaphylaxis. Multiple bee stings can result in systemic toxicity and may require ICU care.

GENERAL MEASURES

» Allergic reactions may be acutely life threatening.
» Patients with multiple stings may develop delayed systemic toxicity. Beware of premature discharge from the healthcare facility.

MEDICINE TREATMENT

Anaphylaxis: See Section 20.7: Anaphylaxis/Anaphylactic Shock.

For pain:

- Paracetamol, oral, 500 mg to 1 g 4 to 6 hourly when required (to a maximum of 4 g in 24 hours). *LoE:IVb*
    - Maximum dose: 15 mg/kg/dose.

19.2 SNAKE BITES

T63.0 + (X20.99/W59.99)

DESCRIPTION

In the majority of snakebite incidents, the offending snake is not identified. The table below illustrates the three main envenomation syndromes seen in South Africa: cytotoxic, neurotoxic and haemotoxic.

	Envenomation syndromes			
	Cytotoxic	**Neurotoxic**	**Mixed cytotoxic & neurotoxic**	**Haemotoxic**
Snake species	Puff adder, Gaboon adder, spitting cobras (Mozambique, black-necked, zebra), stiletto snake, night adders, horned adders	Black and green mamba, non-spitting cobras (Cape, forest, snouted)	Rinkhals, Berg adder, Peringuey's adder, desert mountain adder, garter snakes, shield-nose snake, coral snake	Boomslang, vine snakes
Clinical features of envenomation	Pain, swelling, bruising, blisters, necrosis, regional lymphadenopathy, hypotension, coagulopathy, compartment syndrome	Pins and needles, metallic taste, visual disturbances, ptosis, drowsiness, sweating, drooling, dysphagia, progressive weakness,	Combined cytotoxic and neurotoxic features	Spontaneous bleeding (can present late >24 hours after bite), headaches, dizziness, fainting

		respiratory paralysis		
Antivenom (when indicated)	Polyvalent antivenom for Puff adder, Gaboon adder, and Mozambique spitting cobra only	Polyvalent antivenom for all species	Polyvalent antivenom for rinkhals only	Boomslang monovalent antivenom for boomslang bites only

Table 19.1: Presentation and management of envenomation syndromes
To find pictures for the identification of snakes:
https://journals.co.za/doi/abs/10.10520/EJC126922 or
https://samajournals.co.za/index.php/samj/article/view/1037

LoE:IVb[i]

GENERAL MEASURES

» Most snakebites will not result in death.
» Monitor all cases of snakebite for 24 hours.
» Supportive and symptomatic management with/without antivenom is required.
» Mechanical ventilation may be needed in some cases of neurotoxic envenomation.
» Cases of haemotoxic envenomation may require fluid resuscitation including blood products.
» True compartment syndrome is extremely rare in cytotoxic snakebites, as swelling is localised to the subcutaneous tissues. Fasciotomy is seldom indicated.

MEDICINE TREATMENT

Cleanse wound:

- Chlorhexidine 0.05% in water.

Antibiotics: T79.3 + (X20.99/W59.99)
Antibiotics are seldom indicated unless there is evidence of secondary infection.

- Amoxicillin/clavulanic acid, oral, 875/125 mg 12 hourly for 5 days. A

Immunisation, primary or booster: (Z23.5) *LoE:IVb*[ii]

- Tetanus toxoid vaccine, IM, 0.5 mL immediately, if not previously immunised within the last 5 years.

In unimmunised or partially immunised patients:

- Tetanus immunoglobulin, human, IM, 250 units immediately.

Analgesia

For mild pain:

- Paracetamol, oral, 500 mg to 1 g 4 to 6 hourly when required (to a maximum of 4 g in 24 hours)
    - Maximum dose: 15 mg/kg/dose.

For severe pain:

ADD

- Morphine, IV, to a total maximum dose of 10 mg. (See Appendix II, for individual dosing and monitoring for response and toxicity.). *LoE:IVb*

CAUTION

Opioids increase the risk of respiratory depression particularly for neurotoxic envenomation, and if required, should only be used with caution in severe uncontrolled pain.

Note: NSAIDS are not recommended as they increase the risk of bleeding and renal failure, especially in patients with severe cytotoxic bites.

LoE:IVb[iii]

19.2.1 CYTOTOXIC AND NEUROTOXIC SNAKEBITE

T63.0 + (X20.99/W59.99)

MEDICINE TREATMENT

Polyvalent antivenom

Used in some cytotoxic and neurotoxic envenomations, only where indicated (see indications below).

Available from South African Vaccine Producers (refer to the table above for contact details). See package insert for full details. *LoE:IVb[iv]*

Note:

» In most cases, patients do not need and should not be given antivenom.
» Adverse reactions to antivenom such as allergic reactions (10-30%) are common and may be severe. Pre-medication with adrenaline (epinephrine) may reduce the risk of severe adverse reactions to polyvalent snake antivenom.
» The dose of antivenom is the same for adults and children.
» Monitor for any deterioration in respiratory function as patients may need ventilation whether or not polyvalent antivenom has been given.
» Antivenom should be given as soon as possible, however, administration may be considered even as late as 48-72 hours after the bite if there is continued clinical deterioration that indicates ongoing venom activity.

LoE:IVb[v]

Indications for polyvalent antivenom:

» Signs of neurotoxicity.
» Positively identified puff adder, Gaboon adder, Mozambique spitting cobra or rinkhals bites AND evidence of progressive severe cytotoxicity.
» Unidentified snakebite AND evidence of progressive severe cytotoxicity.
» Severe local cytotoxicity is defined as:

– Swelling of the whole hand or foot within 1 hour.
– Swelling to the knee or elbow in less than 6 hours (or two joints above the bite site in 6 hours).
– Swelling of the whole limb in less than 12 hours.
– Swelling progression > 5 cm/hour.
– Discolouration of the skin / necrosis at the bite site.
– A threatened airway due to swelling.
– Evidence of complications e.g. pseudo- or true compartment syndrome.
– Additional features of severe systemic cytotoxicity include:
  - Haematological abnormalities: Hb <8 g/dL, thrombocytopaenia, (<100 x 10^9/L), raised INR or abnormal thromboelastography (if available).
  - Arrhythmias (rare).
  - Shock

LoE:IIIb[vi]

Note: Polyvalent antivenom is ineffective against the venom of: night adders, berg adders and other smaller adders, boomslang, and vine/twig snakes.

CAUTION
Never administer antivenom without being prepared to manage acute anaphylaxis.

Administration and polyvalent antivenom dose:

- Pre-treat with adrenaline (epinephrine), SC, 0.25 mL of 1:1000 solution.

Note: This is contraindicated in patients with IHD, stroke, uncontrolled hypertension, and tachyarrhythmia.

LoE:IIa[vii]

- Polyvalent snake antivenom, slow IV infusion.
  - This guidance refers to the antivenom produced by South African Vaccine Producers. For any other product refer to the relevant package insert for guidance.
  - 1 ampoule contains 10 mL antivenom.
  - Cytotoxic snakebite (unidentified snake): give 50 mL..
  - For puff adder bites: the initial dose is 80 mL.

LoE:IVb[viii]

LoE:IVb[ix]

- For Mozambique spitting cobras the initial dose is 100 mL.
- Neurotoxic snakebite: give 80–100 mL (and up to 200 mL in black mamba bites).
- Dilute in sodium chloride, 0.9%, 200mL; for example, if 8 ampoules are required, remove 80 mL from 200 ml saline bag and replace with 80 mL antivenom.
- Administer IV, over 30 minutes.
- Reassess once the infusion is completed. A repeat dose may be given if there is ongoing neurotoxicity or cytotoxicity.

19.2.2 BOOMSLANG SNAKEBITE

T63.0 + (X20.99/W59.99)

DESCRIPTION

Boomslang venom is haemotoxic. A consumptive coagulopathy with hypofibrinogenaemia and bleeding usually sets in within 6 to 36 hours after the bite.

GENERAL MEASURES

» In suspected boomslang bite, a whole blood clotting time is a useful bedside test, especially in rural areas. Place 5 mL of blood in a dry glass test tube and leave at room temperature for 20 minutes. Normal clotting time varies from 5–20 minutes. It is important to repeat these over a few days.

» Other investigations include FBC, activated PTT, prothrombin time (INR), fibrinogen, D-dimer, and monomers.

Note: Polyvalent antivenom is not effective in boomslang bites.

Boomslang monovalent antivenom

Indicated for all boomslang bites with evidence of haemotoxicity.

Available from South African Vaccine Producers (refer to the table above for contact details). See full details in the package insert**.**

CAUTION

Never administer antivenom without being fully prepared to manage acute anaphylaxis.

- Boomslang monovalent antivenom, slow IV infusion, 20 mL diluted in 50 to 100 mL sodium chloride, 0.9% or dextrose 5%, administered over 5 to 10 minutes.
  - The dose of antivenom is the same for adults and children.
  - Spontaneous systemic bleeding should stop within 15 to 30 minutes and blood coagulability be restored within 6 hours of administering antivenom. *LoE:IVb[x]*

- Re-evaluate regularly: Consider a repeat dose of 10 ml of antivenom if there is ongoing evidence of coagulopathy after 6 hours.

19.2.3 SNAKE VENOM IN THE EYE

S05.9 + (X20.99/W59.99)

DESCRIPTION

Snake venom in the eye, particularly from various species of spitting cobras and rinkhals, can cause local cytotoxic effects. Clinical presentation ranges from periocular swelling and mild conjunctival and corneal inflammation, to frank corneal ulceration and perforation with eventual blindness.

MEDICINE TREATMENT

Instil local anaesthetic:

- Local anaesthetic ophthalmic drops, e.g.:
- Tetracaine 1%, drops (if available), instil 1 drop into the affected eye(s) before irrigation. *LoE:IIIb*[xi]
  - Irrigate the eye thoroughly for 15–20 minutes with water or sodium chloride, 0.9% to dilute or remove the toxin.

Topical antibiotics:

- Chloramphenicol 1%, ophthalmic ointment 8 hourly for 7 days.
  - Apply chloramphenicol eye ointment and cover the affected eye with an eye patch. *LoE:IVb*

Note: Do not instil polyvalent antivenom in the eye or give systemically.

LoE:IVb[xii]

REFERRAL

Refer all patients to an ophthalmologist.

19.3 SCORPION ENVENOMATION

T63.2 + (X22.99/W59.99)

DESCRIPTION

Medically important scorpions in Southern Africa are of the genus *Parabuthus* (*P. granulatus* and *P. transvaalicus*). These are large scorpions measuring 7–15 cm in length. Features useful in their identification are a relatively large tail and small pincers, so-called thick-tailed scorpions. Scorpions from the *Scorpionidae* family (e.g. *Hadogenes*, *Opistophthalmus*) are thin tailed with large pincers.

To view pictures for the identification of scorpions:
https://journals.co.za/doi/10.10520/EJC126923 *LoE:IVb*[xiii]

A sting from thin-tailed scorpions is likely to result in local pain requiring analgesia only.
Clinical features of thick-tailed scorpion stings include:
Local effects:
» immediate and excruciating pain,
» local paraesthesias and hyperaesthesia.

Systemic effects:
» tremors, involuntary movements and fasciculations,
» muscle pain, cramps, and weakness,
» generalised paraesthesias and hyperaesthesia,
» excessive sympathetic stimulation e.g. sweating, tachycardia,
» excessive parasympathetic stimulation, e.g. hypersalivation, vomiting, diarrhoea, and priapism,
» bulbar paralysis (dysphagia, dysarthria),
» respiratory difficulty/failure.

GENERAL MEASURES
» Observe all cases of thick-tailed scorpion stings for at least 12 hours.
» Monitor respiratory function.
» Ventilatory support may be required.

MEDICINE TREATMENT
Scorpion antivenom therapy is recommended only in cases presenting with systemic neurotoxic effects.
Antivenom available from South African Vaccine Producers (refer to the table above for contact details). See full details in the package insert.

- Scorpion antivenom, IV infusion, 10 mL diluted in 100 mL sodium chloride 0.9% or dextrose 5%, administered over 10 minutes.
    - Response to antivenom may be slow and a repeat dose may be needed.

LoE:IVb

CAUTION
Never administer antivenom without being prepared to manage acute anaphylaxis.

Immunisation, primary or booster: (Z23.5)
- Tetanus toxoid vaccine, IM, 0.5 mL, immediately, if not previously immunised within the last 5 years.

In unimmunised or partially immunised patients: (Z23.5)
- Tetanus immunoglobulin, human, IM, 250 units immediately.

Analgesia

For mild pain:

- Paracetamol, oral, 500 mg to 1 g 4 to 6 hourly when required (to a maximum of 4 g in 24 hours).
    - Maximum dose: 15 mg/kg/dose.

LoE:IVb[xiv]

Severe local pain:

Application of ice, if tolerated.

- Lidocaine 1–2%, 2 mL: infiltrate affected area as a local anaesthetic.

LoE:IVb[xv]

CAUTION

Opiates increase the risk of respiratory depression and if required, should only be used with caution in severe uncontrolled pain.

LoE:IVb[xvi]

Severe muscle pain and cramps:

LoE:IVb[xvii]

- Calcium gluconate 10%, bolus IV infusion, 10 mL over 10 minutes.
    - Repeat if needed, only once i.e. maximum recommended dose of 2 grams.
    - **Note:** Effect may only last for 20 to 30 minutes and there is a limited amount that can be given.

LoE:IVb[xviii]

19.4 SPIDER ENVENOMATION

T63.3 + (X21.99)

DESCRIPTION

Local venomous spiders are divided into cytotoxic and neurotoxic groups.
To view pictures for the identification of spiders:
https://journals.co.za/doi/10.10520/EJC126921

LoE:IVb[xix]

Cytotoxic spider group

The cytotoxic group includes sac, violin, and crab spiders.
Lesions may present with significant bite site necrosis, for which surgical debridement may be required. Bites can take weeks/months to heal.
Note: Antibiotics are reserved for secondary infection.

Neurotoxic spider group

The neurotoxic group is represented by the button spider (also known as widow spiders), genus *Latrodectus*. Black button spiders are more venomous than brown button spiders.

Features useful in the identification of the black button spider are:
» Black or dark brown colour.
» Variable red markings on the dorsal aspect of the abdomen, which diminish with age. It has no ventral markings.

Features of brown button spider:
» Light brown to creamy yellow to pitch black in colour.
» Typical red-orange hourglass-shaped marking on the ventral surface of the abdomen.

Envenomation from black button spiders may cause:
» Immediate local burning pain and tender regional lymph nodes within an hour.
» Severe general muscle pain, cramps, and rigidity especially of the large girdle muscles:
  – Causes feeling of tightness of the chest and board-like rigidity of a non-tender abdomen.
  – Lasts for days to a week if antivenom is not given.
» Profuse sweating may be prominent.
» Diffuse paraesthesia, especially of the hands and feet.

GENERAL MEASURES
Observe all cases of potential neurotoxic spider bite for at least 24 hours.

MEDICINE TREATMENT
» Spider antivenom is only indicated for systemic symptoms of neurotoxicity in patients with button spider bites.
» Antivenom available from South African Vaccine Producers: (refer to the table above for contact details). See full details in the package insert**.**

- Spider antivenom, IV infusion, 5 to 10 mL diluted in 50 to 100 mL sodium chloride, 0.9% or dextrose 5%, administered over 5 to 10 minutes. *LoE:IVb^{xx}*

CAUTION
Never administer antivenom without being prepared to manage acute anaphylaxis.

Immunisation, primary or booster: (Z23.5)
- Tetanus toxoid vaccine, IM, 0.5 mL immediately, if not previously immunised within the last 5 years.

In unimmunised or partially immunised patients: (Z23.5)
- Tetanus immunoglobulin, human, IM, 250 units immediately.

Analgesia

For mild pain:

- Paracetamol, oral, 500 mg to 1 g 4 to 6 hourly when required (to a maximum of 4 g in 24 hours).
    - Maximum dose: 15 mg/kg/dose.

Severe muscle pain and cramps:

- Calcium gluconate 10%, bolus IV infusion, 10 mL over 10 minutes.
    - Repeat if needed, only once, i.e. maximum recommended dose of 2 grams.
    - **Note:** Effect may only last for 20 to 30 minutes and there is a limited amount that can be given.

For secondary infection: *LoE:IVb*[xxi]

See Section 4.2: Cellulitis and Erysipelas.

POISONING

DESCRIPTION

Frequently encountered poisonings in adults are due to:

- analgesics
- anti-infectives
- anticonvulsants
- antihistamines
- cardiodepressants
- iron
- sedatives, antidepressants & antipsychotics
- ethanol/alcohol
- hydrocarbons e.g. paraffin
- irritants and corrosives
- pesticides
- toxic alcohols e.g. methanol, ethylene glycol

Maintain a high index of suspicion for intentional ingestion in adults presenting with poisoning.

DIAGNOSTIC CRITERIA

Clinical

Clinical presentations due to poisoning can be divided into 'toxidromes":

Anticholinergic: e.g. antihistamines, amanita pantherina/muscaria, atropine

- fever
- ileus
- flushing
- tachycardia
- urinary retention
- dry skin and mouth
- blurred vision
- mydriasis (dilated pupils)
- coma
- hallucinations and seizures

Cholinergic: e.g. organophosphates

- salivation
- lacrimation
- urination
- miosis (pinpoint pupils)
- diarrhoea
- vomiting
- bronchorrhoea
- bradycardia

Dystonic: e.g. haloperidol
- » torticollis
- » intermittent spasms and tongue thrusting
- » opisthotonos

Opiates: e.g. morphine
- » miosis (pinpoint pupils)
- » respiratory depression
- » bradycardia
- » altered (decreased) consciousness
- » decreased bowel sounds
- » hypothermia
- » hypotension

Salicylism: e.g. aspirin
- » tachypnoea
- » seizures
- » agitation
- » coma
- » metabolic acidosis and respiratory alkalosis

Sedative-hypnotic: e.g. alcohol, benzodiazepines
- » obtundation or coma

Sympathomimetic: e.g. cocaine, amphetamines
- » hypertension
- » tachycardia
- » hyperthermia
- » agitation
- » sweating
- » dilated pupils

Sympathomimetic toxidrome partially resembles anticholinergic toxidrome, i.e. fight, flight and fright response, however the sympathomimetic toxic patient is sweaty as opposed to hot dry skin seen with anticholinergic toxicity.

Toxic alcohols: e.g. ethylene glycol, methanol
- » metabolic acidosis
- » increased osmolar and anion gaps
- » visual disturbances (methanol)
- » inebriation and depressed level of consciousness.
- » nausea and vomiting
- » tachycardia and arrhythmias
- » renal failure (ethylene glycol)
- » hyperventilation

GENERAL MEASURES

It is very important to ascertain if a potentially TOXIC DOSE has been taken BEFORE instituting any potentially harmful decontamination procedures in an asymptomatic patient.

- » Take a complete and accurate history, ascertain all relevant facts, and do a complete clinical examination.
- » Maintain a high index of suspicion.
- » Obtain a collateral history, especially for patients with impaired consciousness. A special effort should be made to obtain tablets, packets, containers, etc. to identify agents involved.
- » Stabilise the patient and monitor basic clinical parameters, i.e.:
  - – blood pressure and heart rate,

  - hydration,
  - airway and ventilation,
  - neurological status,
  - temperature,
  - glucose.
- » Persistent or prolonged seizures may require medical management. Phenytoin should not be used in cases of poisoning due to substances known to be cardiotoxic e.g. tricyclic antidepressants, or where there is evidence of clinical cardiotoxicity.
- » Prevent physical injury in the restless – avoid excessive sedation. *LoE:IVb*
- » Limit toxicological investigations to those that may influence/alter management. It is important to note the time after ingestion when blood was taken in order to correctly interpret results (e.g. paracetamol and iron levels).

Decontamination

Limit further exposure to poison for the patient and protect healthcare workers where necessary.

Topical exposure

In the case of skin exposure, remove clothes and wash the body. Showering may be useful.

Remove eye contaminants, especially alkalis, acids and other irritants, by continuous irrigation of the eye with sterile water or normal saline for 15 to 20 minutes. Analgesic eye drops may be required to perform this adequately.

Gut decontamination

Methods of gut decontamination include:

- » Gastric lavage.
- » Activated charcoal administration.
- » Whole bowel irrigation.

Gastric lavage

- » If deemed beneficial, it should only be performed by experienced staff and
- » within 60 minutes of ingestion. *LoE:IVb*[xxii]
- » Can be considered for cases with:
  - potentially life-threatening ingestions, AND
  - a protected airway i.e. fully awake and cooperative or intubated with a depressed level of consciousness.
- » Gastric lavage is contra-indicated after ingestion of corrosive substances and volatile hydrocarbons such as paraffin.
- » Technique:
  - Place patient in left lateral head down position.
  - Insert orogastric tube if possible, with largest bore and rounded tip.

- Insert 200mL warmed water or normal saline, and aspirate.
- Continue until recovered solution is clear of particulate matter.

Activated charcoal LoE:IVb[xxiii]

May reduce systemic absorption of a variety of poisonous substances. The greatest benefit is achieved if activated charcoal is given within one hour after ingestion; however, where gastric emptying is delayed by certain substances, there may be a longer period of time in which it is effective. Activated charcoal must only be given in cases where the airway is protected,, i.e. fully awake and cooperative patient or intubated with a depressed level of consciousness.

Activated charcoal may be useful if these poisons are taken in toxic dose	Poisons where charcoal is ineffective and should not be given
» carbamazepine, barbiturates, phenytoin	» ethanol, methanol, ethylene glycol
» dapsone, quinine	» brake fluid
» theophylline	» petroleum products (e.g. petrol or paraffin)
» salicylates	» iron salts
» mushroom poisoning (Amanita phalloides)	» lead, mercury, arsenic
» slow-release preparations	» lithium
» digoxin	» strong acids or alkalis
» beta-blockers	» other corrosive agents (e.g. household detergents)
» NSAIDs	

Table 19.2: Appropriate use of activated charcoal

- Activated charcoal, oral, 50 g (equivalent to 36 level medicine measures) diluted in 100 mL water.
    - When mixing, add a small amount of water to charcoal in a container.
    - Cap and shake container to make a slurry and then dilute further.
    - Repeated doses of activated charcoal (i.e. 50 g every 4 hours) are effective in enhancing elimination of substances that undergo enterohepatic circulation, e.g. carbamazepine, dapsone, phenobarbitone, quinine or theophylline. LoE:IIIb[xxiv]

Whole bowel irrigation

Whole bowel irrigation can be done for potentially toxic ingestions of substances that are:

» not absorbed by activated charcoal (e.g. iron and lithium),
» modified-release and enteric-coated products,
» or for removal of illicit drugs in body packers.

Patients must have a protected airway i.e. fully awake and cooperative or intubated with a depressed level of consciousness.

- Polyethylene glycol (PEG) balanced electrolyte solution, NGT, 1500-2000 mL/hour.
    - Continue until rectal effluent is clear.

LoE:IIIb[xxv]

Other treatment modalities

Sodium bicarbonate alkalinisation

Urine alkalinisation enhances renal elimination of certain toxins (salicylates) and serum alkalinisation improves acidosis enhancing myocardial functioning (TCAs) and reducing neurotoxicity (salicylates).

This is achieved by administering intravenous sodium bicarbonate ($NaHCO_3$) to maintain a urinary pH 7.5-8.5 or serum pH 7.45-7.55.

CAUTION

This is a high-risk procedure and should only be performed in consultation with a specialist.

Haemodialysis

Patients with symptomatically severe poisoning substances including salicylates, lithium, ethylene glycol, methanol, ethanol, and theophylline, may benefit from dialysis (http://www.extrip-workgroup.org/).

Refer patient to a hospital with dialysis facilities.

Antidotes

There are a limited number of antidotes for poisoning by certain substances, e.g. N-acetylcysteine for paracetamol, naloxone for opioids. Each antidote has specific criteria and indications for use.

Once medically stable:

Assess and manage intentional poisoning – self-harm or harm by others:

» Take a history of circumstances around the poisoning, substance use and mental illness, and examine the mental state.
» Assess further suicide risk – see Primary Health Care STGs and EML, Section 16.7: Suicide risk assessment.
» Refer to social, psychological and/or psychiatric services.

Assess and manage a substance use disorder:

» Quantify the amount of substance used and related harms with these rating scales and discuss findings with the patient:
  – ASSIST: https://www.who.int/publications/i/item/978924159938-2
  – DUDIT:https://www.emcdda.europa.eu/system/files/attachments/12173/DUDIT-English-version.pdf
» Provide brief intervention with motivational interview.

» Refer for rehabilitation.

REFERRAL
» Severely ill patient for ventilatory/circulatory support.
» Relevant diagnostic testing not available, e.g. paracetamol levels, acid/base assessment.
» Relevant medication/antidote not available.
» Dialysis/haemoperfusion required.

19.5 ANALGESIC POISONING

19.5.1 PARACETAMOL POISONING
T39.1 + (X40.99/X60.99/Y10.99)

DESCRIPTION
Liver damage, due to the depletion of glutathione and accumulation of toxic metabolites, can occur in any individual with paracetamol overdose. Patients with predisposing risk factors for hepatotoxicity ("high risk" patients, see below) may experience toxicity at lower ingested doses.

Clinical features
Gastrointestinal symptoms (anorexia, nausea, vomiting, malaise) predominate in the first 24 hours. Patients with normal or only slightly raised serum paracetamol levels usually continue to full recovery. In patients with significantly raised paracetamol levels, hepatic toxicity (right upper quadrant abdominal pain and tenderness, elevated bilirubin, raised liver enzymes, coagulation defects, hypoglycaemia, encephalopathy, and metabolic acidosis) may manifest from 20 to 24 hours, peaking in severity at about 72 to 96 hours. Patients may make a full recovery in 5 to 7 days, or demise from hepatic failure, or less commonly, renal failure.

"High risk" patients include those with:
» Chronic alcoholism.
» Chronic liver disease.
» Use of enzyme-inducing medicines (e.g. carbamazepine, phenytoin, efavirenz, phenobarbitone, rifampicin etc.).
» Depletion of glutathione resources (e.g. malnutrition, starvation, AIDS, chronic illness, eating disorders etc.).
» Recent illness, dehydration.

GENERAL MEASURES
The treatment of paracetamol overdose depends on the dose ingested and the time of presentation since ingestion. A serum paracetamol level is plotted on the nomogram to assess the risk for hepatotoxicity. Values which appear above the treatment line require the antidote N-acetylcysteine (NAC).

Acute single ingestion <8 hours post-ingestion:

» Toxic dose is defined as a paracetamol ingestion >200 mg/kg or 10 g (whichever is less).
» Give activated charcoal if the patient presents within 1-2 hours of ingestion.
» Perform a serum paracetamol level and ALT no earlier than 4 hours post-ingestion.
» If serum paracetamol level results will not be available before 8 hours post-ingestion, AND the patient has taken a toxic dose, do not delay initiation of NAC. It can always be stopped if the serum level plotted on the nomogram does not indicate its continued use.

Acute single ingestion >8 hours post-ingestion:

» Toxic dose defined as >200 mg/kg or 10 g (whichever is less).
» Start NAC infusion if a toxic dose has been ingested or the patient shows clinical signs of toxicity.
» Perform serum paracetamol level, ALT, and INR.
» Indications for continuing NAC infusion:
  – Serum paracetamol level above the treatment line on the nomogram.
  – Serum paracetamol level under the treatment line but abnormal ALT.
  – Measurable paracetamol level and/or abnormal ALT more than 24 hours post-ingestion.

Acute single ingestion with unknown time of ingestion:

Manage as for >8 hours post-ingestion, however, the nomogram is not applicable to this group.

LoE:IIIa[xxvi]

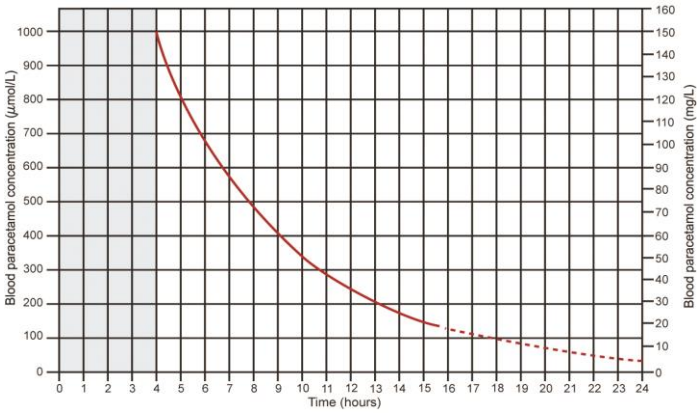
Repeated supratherapeutic ingestion (RSTI):

This may occur in patients using repeated high doses of the same product or concurrent use of multiple paracetamol-containing products such as during an acute febrile illness or in patients with chronic pain.

RSTI toxic doses are defined as:

» >200 mg/kg or 10 g (whichever is less) over a single 24-hour period.
» >300 mg/kg or 12 g (whichever is less) over a single 48-hour period.
» >60 mg/kg/day for more than 48 hours ***and*** patients have symptoms suggestive of liver injury.

LoE:IIIa[xxvii]



Source: Daly FF, Fountain JS, Murray L, Graudins A, Buckley NA; Panel of Australian and New Zealand clinical toxicologists. Guidelines for the management of paracetamol poisoning in Australia and New Zealand-explanation and elaboration. A consensus statement from clinical toxicologists consulting to the Australasian poisons information centres. Med J Aust. 2008 Mar 3;188(5):296-301.

Figure 19.1: Paracetamol treatment nomogram. (Access the paracetamol nomogram tool on the EML Clinical Guide Smartphone application.).

MEDICINE TREATMENT

N-acetylcysteine is the antidote of choice and should be given intravenously. Although it is more effective when given within 8 hours of ingestion of paracetamol, there may be benefit even if liver failure has developed. Histamine may be released, which mimics an allergic reaction. If this occurs and the patient is stable, infusion may continue at a slower rate under antihistamine cover. Stop the infusion if bronchospasm occurs.

- N-acetylcysteine, IV:
  - Initial infusion: 200 mg/kg in 500 mL dextrose, 5% over 4 hours.
  - Second infusion: 100 mg/kg in 1000 mL dextrose, 5% over 16 hours.
  - Any further N-acetylcysteine is given according to the second infusion regimen.

LoE:IIIa[xxviii]

<u>If N-acetylcysteine IV formulation is unavailable:</u>

- N-acetylcysteine, oral, 140 mg/kg immediately.
  - Followed by 70 mg/kg 4 hourly, for up to seventeen doses.

LoE:IIIa[xxix]

Note:

» As anaphylactoid reactions to N-acetylcysteine do occur, the loading dose should preferably be administered in a monitored area.

LoE:IVb[xxx]

» Avoid giving oral N-acetylcysteine together with activated charcoal as systemic absorption and effect of N-acetylcysteine is reduced.

LoE:IIIa[xxxi]

Further investigations and referral
Blood tests such as renal function, clotting profile, serum glucose and acid/base status should only be done where clinically indicated.
Patients who develop liver failure must be referred for further management and/or possible transplant.

19.5.2 SALICYLATE POISONING

T39.0 + (X40.99/X60.99/Y10.99)

DESCRIPTION

Salicylate poisoning may result from oral and/or topical exposure. Salicylate products vary widely in concentration, e.g. oil of wintergreen is almost 100% methyl salicylate.

Diagnosis:
Mild to moderate toxicity:
» Nausea, vomiting, tinnitus, fever, tachypnoea, and respiratory alkalosis

Severe toxicity:
» Metabolic acidosis, altered mental status, seizures, coma, non-cardiogenic pulmonary oedema.
» Monitor salicylate levels if possible (do not always correlate with clinical severity):

Severity of toxicity	Peak plasma salicylate concentrations	
	mmol/L	mg/dL
Asymptomatic	<2.2 mmol/L	<30 mg/dL
Mild toxicity	2.2-4.3 mmol/L	30-60 mg/dL
Moderate toxicity	4.3-5.8 mmol/L	60-80 mg/dL
Severe toxicity	>5.8 mmol/L	>80 mg/dL

Table 19.3: Severity of toxicity by peak plasma salicylate concentrations.

» Serial monitoring until declining levels are documented.
» Monitor and treat hypoglycaemia; patients with normoglycaemia may still be neuroglycopaenic.

GENERAL MEASURES

» Assess severity with history, clinical examination, and salicylate levels if possible.
» Correct hydration using dextrose-containing fluids.
» Ensure hypokalaemia treated early
» Consider ICU admission for pulmonary and/or cerebral oedema.

MEDICINE TREATMENT

- Salicylates delay gastric emptying, therefore activated charcoal may be effective for a longer period than usual.

- Whole bowel irrigation maybe useful for enteric-coated or modified-release preparations. *LoE:IIIb*[xxxii]

For mild toxicity:

» Rehydrate and correct hypovolaemia with dextrose-containing fluids.
  - Add dextrose 50%, 100mL to every litre of balanced crystalloid solution (e.g. Ringer'sR' lactate) or sodium chloride 0.9% and administer by IV infusion. *LoE:IIIb*[xxxiii]
  - During preparation of the infusion fluid, ensure the equivalent volume of rehydration fluid (e.g. 100mL) is removed from the bag before adding the total dextrose 50% volume (e.g. 100 mL).
  - The rate and duration of IV fluids should be guided by clinical assessment of fluid balance. *LoE:IVb*

In patients with moderate to severe toxicity and/or acidosis:

- Sodium bicarbonate 8.4%, IV, 1–2 mL/kg over 30 minutes to manage acidosis. *LoE:IIIb*[xxxiv]
- Simultaneously fluid resuscitate with sodium bicarbonate 8.4%, 150 mL added to dextrose 5%, 1 L and administer by IV infusion to correct hypovolaemia.
  - During preparation of the infusion fluid, ensure the equivalent volume of dextrose 5% (i.e. 150 mL) is removed from the bag before adding the total sodium bicarbonate 8.4% volume of 150 mL.
  - Continue a maintenance infusion at 150 to 200 mL/hour, targeting a urine output of 2 mL/kg/hour.
  - Titrate the sodium bicarbonate maintenance infusion to a urinary pH of 7.5 to 8.5 and blood pH of 7.45 to 7.5.
  - Monitor for and correct hypokalaemia. *LoE:IVb*

REFERRAL

» Discuss with specialist and consider ICU admission.
» Where acidosis does not respond to sodium bicarbonate, refer for haemodialysis. *LoE:IIIa*[xxxv]

19.5.3. OPIOID POISONING

T40.0/T40.1/T40.2/T40.3 + (X42.99/X62.99/Y12.99)

DESCRIPTION

Patients present with the triad of CNS depression, respiratory depression, and constricted pupils. Non-cardiogenic pulmonary oedema can occur.

GENERAL MEASURES

Supportive management aimed at maintaining cardiorespiratory function.

Body packers/stuffers:

» Patients may ingest packages of illicit opioids and are at increased risk of life-threatening toxicity in the event of rupture.
» Abdominal X-rays or CT scan may show packages.
» Conservative management is recommended, as any attempt at removal risks package rupture.
» Activated charcoal and whole bowel irrigation may aid in expelling packets.
» Surgery is reserved for those who develop obstruction or perforation.

MEDICINE TREATMENT

- Naloxone, IV, 0.4 mg immediately, in patients with significant respiratory depression.
    - Effectiveness is limited by a half-life (± 1 hour) that is shorter than most opioids.
    - Repeated incremental doses (e.g.: 0.4 mg, 0.8 mg, 2 mg, 4 mg etc.) may be required at 2-to-3-minute intervals, up to a maximum of 10 mg. If a response is noted, a maintenance infusion of 0.4 mg/hour should be initiated.
    - If there is no response after a maximum total dose of 10 mg of naloxone is administered, the diagnosis of opioid-induced or partial opioid-induced toxicity should be re-assessed.
    - Consider intramuscular or subcutaneous administration if the intravenous route is not available.

Note:

- Clinical response is measured by reversal of respiratory depression rather than complete reversal of sedation.
- Continuous monitoring is required for all patients who receive naloxone.
- Naloxone in an opioid-dependent person may precipitate a withdrawal syndrome with agitation, hypertension, tachycardia, emesis, and potential aspiration. These patients usually require lower doses when initiating naloxone (0.04 to 0.1 mg IV).

LoE:IVb[xxxvi]

19.6 ANTIDEPRESSANT POISONING

19.6.1. TRICYCLIC ANTIDEPRESSANT POISONING

T43.0 + (X41.99/X61.99/Y11.99)

DESCRIPTION

TCAs may be life threatening at relatively low doses. Cardiovascular and neurological impairment are the most serious consequences of TCA toxicity, and patients can deteriorate rapidly depending on the severity.

LoE:IVb[xxxvii]

Mild to moderate poisoning:
» Sedation.
» Anticholinergic effects:
- delirium,
- tachycardia
- dilated pupils
- urinary retention
- dry mouth

Severe Poisoning:
» Widened QRS duration, ventricular dysrhythmias
» Coma
» Hypotension
» Seizures
» Pulmonary oedema

GENERAL MEASURES
» Do a baseline ECG in all patients.
» ICU admission for ventilatory/circulatory support, when indicated. Be prepared to intubate symptomatic patients early.
» Discharge patients only when:
– asymptomatic, or
– mild symptoms/signs of toxicity and ECG has normalised for at least 24 hours.

MEDICINE TREATMENT
Tricyclic antidepressants delay gastric emptying, therefore activated charcoal may be effective for a longer period than usual.
Indications for serum alkalinisation:
» ventricular dysrhythmias,
» prolonged QRS >100 msec,
» hypotension unresponsive to fluids, or
» seizures.

- Sodium bicarbonate 8.4% solution, IV 1 to 2 mL/kg administered in bolus doses. (Specialist consultation).
  - Aim to achieve a serum pH of 7.45 to 7.55.
  - Monitor acid-base status, serum potassium and sodium.
  - If sodium bicarbonate is unavailable or fluid restrictions limit intake, consider hyperventilation of intubated patients. *LoE:IIIa*[xxxviii]

LoE:IVb

In severe cases, inotropic support and anti-arrhythmics may be required (see Section 3.3: Cardiac dysrhythmias) in addition to serum alkalinisation. Hypotension is due to myocardial dysfunction and alpha-adrenergic vasodilation; be careful not to fluid overload the patient.

For seizures or if sedation is required for restlessness:
Treat with benzodiazepines - see Section 14.5: Status epilepticus.
Note: Phenytoin should be avoided (due to potential cardiotoxicity).

LoE:IVb[xxxix]

LoE:Ia[xl]

Note: Flumazenil is not recommended in any patient with mixed overdoses possibly including tricyclic antidepressants as it increases the risk of convulsions and dysrhythmias.

19.7 IRON POISONING

T45.4 + (X44.99/X64.99/Y14.99)

DESCRIPTION

Iron is a commonly prescribed drug, especially in pregnancy, and in overdose causes initial gastrointestinal toxicity. Patients may have a stage of "apparent recovery" 6–36 hours post-ingestion. This should not be confused with true recovery as patients may subsequently deteriorate.

Significant exposure may be associated with:

- » severe vomiting and diarrhoea
- » metabolic acidosis,
- » CNS depression,
- » hepatitis.
- » gastrointestinal haemorrhage
- » hypotension, shock
- » renal failure, and

Ferrous salt	Amount	Elemental iron
Ferrous sulphate	170 mg	± 65 mg
Ferrous gluconate	300 mg	35 mg
Ferrous fumarate	200 mg	± 65 mg

Table 19.4: Elemental iron content available in different iron salts

GENERAL MEASURES

- » Gastrointestinal decontamination by whole bowel irrigation is recommended:
  - – if >60 mg/kg elemental iron has been ingested,
  - – if modified-release preparations ingested,
  - – undissoved tablets still visible on abdominal X-ray.
- » Activated charcoal does not bind iron and is not indicated in isolated iron overdose.
- » Serum iron concentration should be measured 4–6 hours after ingestion and repeated every 6 hours until peak. The use of deferoxamine (desferrioxamine) interferes with the interpretation of further serum iron levels.
- » Give intravenous fluids for hypotension.

MEDICINE TREATMENT

Chelation therapy

» Patients with serum iron levels <54 µmol/L and absence of symptoms >6 hours after overdose do not require chelation therapy.

» Deferoxamine (desferrioxamine) may be used for the following indications (if in doubt, consult the Poisons Information Helpline):
  – Severe symptoms (altered mental status, haemodynamic instability, metabolic acidosis).
  – Serum iron concentration >90 µmol/L.
  – Peak serum iron concentration >60 µmol/L, AND persistent gastrointestinal symptoms.

LoE:IIIa[xli]

- Deferoxamine (desferrioxamine), IV infusion, 80 mg/kg. *LoE:IVb*[xlii]
  - Administer at 15 mg/kg/hour over about 6 hours.
  - Beware of hypotension.
  - **Note:** Prolonged use (>24 hours) of high doses is associated with acute lung injury and should be avoided. However, additional doses may be required in severe poisonings – aa benefit-risk assessment is required in these patients.
  - Where IV access is not obtainable, deferoxamine can be given by IM injection as follows: deferoxamine, IM injection 1 g immediately, followed by 500 mg every 4 to 12 hours, as needed based on clinical response.
  - For cardiogenic shock, the IV route is preferred and should be used as soon as IV access is possible. *LoE:IIIa*[xliii]
  - Deferoxamine can be used in pregnant women.

REFERRAL

Haemodialysis may be needed to remove deferoxamine-iron complexes in patients with renal insufficiency.

19.8 THEOPHYLLINE POISONING

T48.6 + (X44.99/X64.99/Y14.99)

DESCRIPTION

Patients present with:

» tachycardia and tachyarrhythmias,
» nausea and vomiting
» agitation
» seizures
» hyperventilation
» tremor
» profound hypokalaemia
»

GENERAL MEASURES

» Monitor ECG and treat dysrhythmias.
» Monitor and correct fluid status and electrolyte abnormalities.
» Monitor theophylline concentrations, if available. Levels may continue to rise up to 24 hours after ingestion of modified release preparations.

MEDICINE TREATMENT

- Activated charcoal, oral, 50 g diluted in 100 mL water.
    - Multiple doses of activated charcoal enhance elimination.

LoE:IIIa[xliv]

Vomiting is common: (R11)

LoE:IVb

- Metoclopramide, IV/oral, 10 mg 8 hourly as required.

Correct hypokalaemia cautiously: E87.6 + (T48.6+X44.99/X64.99/Y14.99)

- Potassium chloride, IV, 20 to 40 mmol/L in sodium chloride, 0.9%.
    - Maximum rate of infusion: 20 mmol/hour.

LoE:IIIa[xliv]

For seizures: R56.8 + (T48.6+X44.99/X64.99/Y14.99)
Treat with benzodiazepines - see Section 14.5: Status epilepticus.
Note: Phenytoin should be avoided (due to potential cardiotoxicity).

LoE:IVb[xlvi]

REFERRAL

In patients with symptoms of severe overdose (severe hypokalaemia, seizures, refractory hypotension, dysrhythmias, theophylline level >555 µmol/L (100 mg/L), refer for haemodialysis.

LoE:IIIa[xlvii]

19.9 SEDATIVE HYPNOTIC POISONING

19.9.1 BENZODIAZEPINE POISONING

T42.4 + (X41.99/X61.99/Y11.99)

DESCRIPTION

Patients present with depressed levels of consciousness, confusion, ataxia, and dysarthria. Benzodiazepines are unlikely to cause significant respiratory depression unless co-ingested with alcohol or other CNS depressants. However, there is a risk of respiratory depression due to overdose in the elderly.

GENERAL MEASURES

Management is supportive, and ventilation may be required.

Note: The use of flumazenil is not recommended in any patient with possible benzodiazepine poisoning as it increases the risk of convulsions and dysrhythmias.

LoE:Ia[xlviii]

19.9.2 LITHIUM POISONING

T43.8 + (X41.99/X61.99/Y11.99)

DESCRIPTION

Lithium toxicity mostly occurs with chronic therapy and may be precipitated by decreased excretion due to renal dysfunction, diuresis, dehydration, hyponatraemia, or drug-drug interactions (e.g. NSAIDs, diuretics, ACE-inhibitors, and ARBs).

Signs and symptoms include:

- » nausea, vomiting, and diarrhoea
- » nystagmus
- » CNS symptoms: tremor, hyperreflexia, choreoathetoid movements, fasciculations, ataxia, agitation, confusion and lethargy

In severe toxicity:

- » Coma
- » Seizures
- » Dysrhythmias
- » Hypotension

GENERAL MEASURES

Monitor:

- » Vitals signs, mental status, and urine output.
- » If available, do serial lithium levels 6 hourly until peaked and declining.
- » Electrolytes and renal function.
- » Cardiac function and treat dysrhythmias (see chapter 3.3: Cardiovascular dysrhythmias).
- » Thyroid function, in chronic toxicity.

MEDICINE TREATMENT

If ingested dose is potentially toxic or modified-release products were ingested, consider WBI.

LoE:IIIb[xlix]

- » Hydration: administer sodium chloride, 0.9 % to maintain urine flow of 1 to 2 mL/kg/hour while preventing hypernatremia.
- » Correct electrolyte abnormalities: see Section 7.2: Major electrolyte abnormalities.
- » For seizures: Treat with benzodiazepines – see Section 14.5: Status epilepticus.

Note: Phenytoin should be avoided (due to potential cardiotoxicity).

REFERRAL

LoE:IVb[i]

Early referral for haemodialysis is indicated in severe lithium poisoning and in patients with renal impairment. Discuss with a specialist.

LoE:IIIa[ii]

19.10 ISONIAZID POISONING

T37.1 + (X44.99/X64.99/Y14.99)

DESCRIPTION

Acute toxicity can present with the classic triad of seizures, metabolic acidosis, and coma. Seizures are of a generalised tonic-clonic type, and often refractory to standard anticonvulsant therapy.

GENERAL MEASURES

Supportive management aimed at preventing and managing complications. Treat hyperthermia.

MEDICINE TREATMENT

For seizures:

- Pyridoxine, crushed tablets orally or via NGT in unconscious patient(s).
    - Known amount: Pyridoxine dose is 1 g for every gram of isoniazid ingested (maximum of 5 g)
    - Unknown amount: Pyridoxine dose is 5 g for unknown amount ingested.

LoE:IIIa[iii]

Benzodiazepines may be used as an interim measure to control seizures:

- Lorazepam, IV/IM, 4 mg, repeat once after 5–10 minutes, if necessary.

LoE:IVb[iii]

OR

- Diazepam, IV, 10 mg, not faster than 2 mg/minute, repeat once after 5 to 10 minutes if necessary.

OR

- Clonazepam, IV, 2 mg, repeat once after 5 to 10 minutes if necessary.

OR

- Midazolam, IM/IV 10 mg, repeat once after 5 to 10 minutes if necessary.

OR

- Midazolam buccal, 10 mg using the parenteral formulation.

CAUTION

Phenytoin should not be used to control seizures in INH poisoning, as it does not have GABA agonist properties.

LoE:IVb[iv]

REFERRAL
» Uncontrolled seizures.

19.11 CALCIUM CHANNEL BLOCKER AND BETA BLOCKER POISONING
T44.7/T46.1 + (X43.99/X63.99/Y14.99)

DESCRIPTION
Cardiovascular toxicity results in profound hypotension, bradycardia, decreased systemic vascular resistance and cardiogenic shock. Depressed level of consciousness and metabolic acidosis are due to poor tissue perfusion. Hyperglycaemia and hypokalaemia may occur. Patients who have co-ingested other cardiac medicines and those with pre-existing cardiac disease are at increased risk of morbidity.

The treatment of suspected cardiogenic shock in calcium channel blocker and beta blocker poisoning follows similar therapeutic principles. The mainstay of treatment is high-dose insulin euglycaemic therapy (HIET) and inotrope and vasopressor infusions.

GENERAL MEASURES
» Monitor vital signs, ECG, and blood glucose. *LoE:IVb[iv]*
» Treat symptomatic patients in consultation with a specialist.

MEDICINE TREATMENT
» Caution is advised for all decontamination procedures as they increase vagal tone and may exacerbate bradycardia.
» Activated charcoal may be considered before the onset of symptoms.
» Whole bowel irrigation can be considered for ingestion of modified-release preparations. *LoE:IIIa[vi]*

Bradycardia: R00.1 + (T46.1/X44.99/X64.99/Y14.99)
- Atropine, IV 0.5 to 1 mg every 2 to 3 minutes to a maximum of 3 mg. *LoE:IVb[vii]*

Hypotension: I95.9 + (T46.1/X44.99/X64.99/Y14.99)
- Start with sodium chloride 0.9%, IV. *LoE:IVb[viii]*

If not effectively controlled

ADD
- Calcium gluconate 10%, IV, 30 to 60 mL given over 15 to 30 minutes, with ECG monitoring.
  - This may be repeated a maximum of 4 times. *LoE:IVb[ix]*
- Simultaneously use vasopressors and inotropes as needed, e.g. adrenaline (epinephrine) infusion for persistent hypotension (Section 20.1:

Cardiac arrest in adults) or dobutamine for bradycardia (Section 20.11.3: Cardiogenic shock) and refer patient immediately.

REFERRAL
All patients requiring HIET should be treated in a High Care or ICU setting.

19.12 COTRIMOXAZOLE POISONING
T37.0 + (X44.99/X64.99/Y14.99)

DESCRIPTION
Acute overdose is associated with a low probability of clinically relevant toxicity. Symptoms include nausea and vomiting, dizziness, headache, and neurological symptoms (such as drowsiness, confusion, and mental depression). Other signs include bone marrow depression, haematuria, and renal insufficiency. Hypersensitivity reactions may occur.

GENERAL MEASURES
» Treatment is symptomatic and supportive.
» Monitor FBC, electrolytes, glucose, hepatic, and renal function in symptomatic patients.

19.13 ANTIRETROVIRAL AGENTS POISONING
T37.5 + (X44.99/X64.99/Y14.99)

DESCRIPTION
» Limited data is available regarding overdose of these medicines.
» Toxicological effects are generally extensions of their adverse effects.

GENERAL MEASURES
» Monitor FBC, serum electrolytes, renal and liver function.
» Monitor serum lipase in patients with abdominal pain.
» Lactic acid and serum pH should be monitored in acidotic patients.

TREATMENT
» There are no specific antidotes.
» Treatment is symptomatic and supportive.

19.14 ILLICIT DRUGS

19.14.1 COCAINE POISONING

T40.5 + (X42.99/X62.99/Y12.99)

DESCRIPTION

Cocaine may be absorbed through any mucous membrane, smoked, ingested, or injected intravenously.

Clinical features:

Mild toxicity*:* euphoria, anxiety, altered mental status, tachycardia, mild hypertension.

Moderate toxicity: agitation, paranoia, hallucinations, cardiac dysrhythmias.

Severe toxicity*:* severe headache, seizure, hyperthermia, rhabdomyolysis, severe acidosis, vascular incidents (stroke, MI, intestinal ischaemia etc.), pulmonary oedema.

GENERAL MEASURES

» Supportive management aimed at preventing and managing complications.
» Cool patients with hyperthermia.
» Raised serum creatinine kinase may indicate rhabdomyolysis or myocardial infarction.

» Body packers/stuffers:
  – Patients may ingest packages of cocaine and are at increased risk of life-threatening toxicity in the event of rupture.
  – Abdominal X-rays or CT scan may be helpful in identifying packages.
  – Conservative management is recommended, as any attempt at removal risks package rupture.
  – Activated charcoal and whole bowel irrigation may aid in expelling packets.
  – Surgery is reserved for those who develop obstruction or perforation.

MEDICINE TREATMENT

Benzodiazepines play a key role in the management of sympathetic and psychomotor features of cocaine poisoning.

For sedation and seizures:

Treat with benzodiazepines - see Section 14.5: Status epilepticus.

Note: Phenytoin should be avoided (due to potential cardiotoxicity).

LoE:IVb[x]

Delirium with severe agitation:

See Section 20.8: Delirium.

Arrhythmias:
See Section 3.3: Cardiac dysrhythmias.

Hypertension unresponsive to benzodiazepines:
See Section 3.6: Hypertension

CAUTION
ß–blockers (other than labetalol) may worsen vasoconstriction and should not be used.

19.14.2 AMPHETAMINE DERIVATIVES POISONING

T43.6 + (X41.99/X61.99/Y11.99)

DESCRIPTION

These include:
» "Ecstasy": 3,4-methylenedioxymethamphetamine (MDMA).
» "Ice" and "Eve": 3,4-methylenedioxy-N-ethylamphetamine (MDEA).
» "Tik": Methamphetamine.

Drug effects are due to the increased release of noradrenaline, dopamine, and serotonin. Patients present with:
» hyperthermia, especially with MDMA
» tachycardia
» hypertension
» angina pectoris and myocardial infarction
» stroke
» hyperactivity
» sweating
» dilated pupils
» teeth grinding
» delirium
» tremors
» seizures and coma

Additional complications include:
» rhabdomyolysis
» hyperkalaemia
» acute tubular necrosis
» hyponatraemia
» dehydration

GENERAL MEASURES

Supportive management aims to maintain stable cardiorespiratory function. Manage hyperthermia, hypoglycaemia, dehydration, and electrolyte abnormalities.

MEDICINE TREATMENT

LoE:IVb[lxi]

For seizures: R56.8 + (T43.6 + X41.99/X61.99/Y11.99)
Treat with benzodiazepines - see Section 14.5: Status epilepticus.
Note: Phenytoin should be avoided (due to potential cardiotoxicity).

Severe hypertension:
See Section 3.6.1: Hypertension, asymptomatic severe.

Haemodialysis may be required for acute renal failure.

19.15 HYDROCARBON POISONING

T52.0 + (X46.99/X66.99/Y16.99)

Note: This section does not include information on aromatic hydrocarbons (e.g. benzene, toluene, xylene) often used by glue sniffers to get high.

DESCRIPTION

Poisoning due to petroleum products, including paraffin, turpentine, petrol, and mineral spirits.

Clinical signs include:

- » chemical pneumonitis
- » arrhythmias
- » nausea and vomiting
- depression, seizures, coma

GENERAL MEASURES

- » If contaminated, remove clothing and wash skin.
- » Do not induce emesis or attempt gastric emptying/lavage.

MEDICINE TREATMENT

- » Activated charcoal is of no value.
- » Observe and examine for chemical pneumonitis. Prophylactic antibiotics are not indicated.

19.16 INGESTION OF CAUSTIC SUBSTANCES

T54.1A/T54.2/T54.3/T54.9 + (X46.99/X66.99/Y16.99)

DESCRIPTION

- » Alkaline: Toilet bowl cleaners, drain cleaners, oven cleaners.
- » Acids: Various e.g. domestic descalers.
- » Caustic substances can cause necrosis of the gut mucosa and underlying tissue, resulting in acute perforation (particularly strong alkalis), and possible strictures later (which can occur with acids and alkalis). Concentrated caustic substances are more corrosive and present a higher risk for necrosis.

GENERAL MEASURES

- » No activated charcoal, forced emesis, or gastric lavage.
- » Rinse mouth with copious amounts of cold water.
- » Make patient nil by mouth and set up IV access.
- » If persistent vomiting, drooling or any difficulty in swallowing, patient may require endoscopic evaluation within 24-48 hours and possible surgical intervention. (Discuss with a specialist).

LoE:Ivb[lxii]

19.17 ALCOHOLS

19.17.1 ETHANOL POISONING

T51.0 + (X45.99/X65.99/Y15.99)

DESCRIPTION

Acute poisoning usually presents with:

- » Nausea and vomiting
- » Hypoglycaemia
- » Hypokalaemia
- » Depression, seizures, coma
- » Hypothermia
- » Acidosis

Consider other causes for the patient's condition, including hypoglycaemia and head trauma.

GENERAL MEASURES

- » Supportive management is aimed at maintaining stable cardiorespiratory function.
- » Protect the airway (ventilation may be needed).
- » Manage hypothermia, hypoglycaemia, and electrolyte abnormalities.

MEDICINE TREATMENT

- Thiamine, IV, 100 mg in 1 L dextrose, 5%.

19.17.2 ETHYLENE GLYCOL POISONING

T52.3 + (X46.99/X66.99/Y16.99)

DESCRIPTION

Ethylene glycol is the main component of motor vehicle radiator coolant/antifreeze and is occasionally found in brake fluid. It is also found in homemade toilet and drain cleaners.

Mild to moderate intoxication: resembles alcohol intoxication, with nausea and vomiting, nystagmus, ataxia, and somnolence.

Severe intoxication: associated with more severe CNS depression (coma, hypotonia, hyporeflexia) and high anion gap metabolic acidosis. Cardiovascular signs include tachycardia and hypertension. Calcium oxalate crystals cause renal failure and hypocalcaemia, which may manifest with prolongation of the QT interval on ECG or tetany.

$$Anion\ gap = Na - (CL + HCO_3)\ [Normal = 8 - 16]$$

GENERAL MEASURES

- » Consult the Poisons Information Helpline for assistance with management.

» Treat early to reduce the risk of forming toxic metabolites.
» Monitor blood gases and administer sodium bicarbonate.
» Early haemodialysis is the treatment of choice for severe poisoning with profound acidosis.

MEDICINE TREATMENT

Ethanol

LoE:Ivb[xiii]

Indications:

History of ingestion, plus any two of the following criteria:

» Arterial pH <7.3.
» Serum bicarbonate <20 mmol/L.
» Presence of urinary oxalate crystals (ethylene glycol only) or visual disturbances (methanol only).

Preparation and administration of ethanol:

Step 1: Prepare an ethanol 20% solution:

If using Ethanol 96% BP, oral,

- Add 1 part ethanol 96% to 4 parts juice or water e.g. 250 mL of ethanol 96% with 1000mL water or juice to give a total volume of 1250 mL ethanol 20%.

If using Ethanol 40% v/v (gin, whiskey, vodka), oral

- Add 1 part ethanol 40% to 1 part juice or water e.g. dilute 500 mL of ethanol 40% with 500 mL water or juice to give a total volume of 1000 mL ethanol 20%.
- **Note:** Spirit liquor products in South Africa are frequently bottled at 43% v/v. These can be used interchangeably.

Step 2: Administer a loading dose:

- Ethanol 20% (the solution prepared in Step 1), oral, 4 mL/kg over 15-30 minutes.

Step 3: Continue with maintenance doses:

- Ethanol 20% (the solution prepared in Step 1), oral:
  - Non-drinker: 0.5 mL/kg/hour.
  - Chronic drinker: 1 mL/kg/hour.

WORKED EXAMPLES

For a 60kg patient who is a non-drinker:

Loading dose: 240 ml of the ethanol 20% solution orally over 15 to 30 minutes.

Maintenance dose: 30 mL per hour orally of the ethanol 20% solution.

For a 60kg patient who is a chronic drinker:

Loading dose: 240 ml of the ethanol 20% solution orally over 15 to 30 minutes.

Maintenance dose: 60 mL per hour orally of the ethanol 20% solution.

Note:
» If patients are not co-operative, administer ethanol via a nasogastric tube.

CAUTION
Locally available commercial ethanol products are not approved for IV administration and should not be administered via this route.

» Maintain ethanol levels of 1 to 1.3 g/L (100 to 130 mg/dL).
» Where ethylene glycol, methanol (see Section 19.17.3: Methanol poisoning), and ethanol levels are not available for monitoring purposes, titrate the ethanol rate of administration according to improvement in metabolic acidosis and signs of systemic toxicity.
» Increase the dose of ethanol if the patient is receiving concomitant haemodialysis.
» Several days of ethanol therapy may be required until clinical condition improves.
» Alcoholic beverages are sometimes labelled as "percentage proof". Alcohol proof values are double the alcohol percentage (volume/volume) values. i.e. an 80 proof alcohol would be 40% (v/v).

Cofactor therapy: *LoE:IVb[lxiv]*
- Thiamine, oral, 100 mg daily.
- Pyridoxine, oral, 100 mg daily.

Metabolic acidosis: E87.2 + (T52.8/X46.99/X66.99/Y16.99) *LoE:IVb[lxv]*
- Sodium bicarbonate 8.4%, IV, 50–100 mmol/L administered over 30–45 minutes.

Note:
» Rapid correction of acidosis may precipitate seizures in a hypocalcaemic patient. Correct severe or clinically evident hypocalcaemia.
» Monitor glucose levels and correct hypoglycaemia, if necessary. *LoE:IVb[lxvi]*

REFERRAL
Severe poisoning with profound acidosis for early haemodialysis.

19.17.3 METHANOL POISONING
T51.1 + (X45.99/X65.99/Y15.99)

DESCRIPTION
Methanol, once present in methylated spirits, was replaced with less toxic agents 10-20 years ago. However, it may still be found in stove or model fuels, as well as in antifreeze and windscreen washes.

Presentation:
» Ingestion of methanol results in initial mild inebriation (headache, confusion, nausea, and vomiting) similar to ethanol intoxication followed by an asymptomatic/latent period.
» After a latent period of about 12-24 hours, toxic metabolite (formic acid) formation results in severe high anion gap metabolic acidosis, and retinal toxicity (from visual impairment to total blindness).

$$Anion\ gap = Na - (CL + HCO_3)\ [Normal = 8 - 16]$$

MEDICINE TREATMENT
If acidotic or patient has visual disturbances;
Start with immediate ethanol antidote therapy (See Section 19.17.2: Ethylene glycol poisoning), and evaluate for urgent dialysis, if available.

LoE:IIIa[lxvii]

19.18 PESTICIDES AND RODENTICIDES

19.18.1 AMITRAZ POISONING
T44.4 + (X43.99/X63.99/Y13.99)
* Notifiable condition.
Poisoning from all pesticides (i.e. agricultural stock remedies) is a notifiable medical condition. Please visit https://www.nicd.ac.za/nmc-overview/notification-process/ for further information.

DESCRIPTION
Amitraz is a pesticide/insecticide with α_2-adrenergic agonist properties. It is usually formulated as a tick dip for dogs, cattle, and sheep. Commercial formulations contain up to 20% of amitraz in organic solvents. Poisoning may occur when amitraz is ingested or absorbed via the skin or by inhalation.

A history of an unspecified rat poison or pesticide exposure warrants consideration of other active ingredients such as super-warfarin anticoagulants and organophosphates.

Patients with acute poisoning present with:
» impaired consciousness
» drowsiness
» vomiting
» hypotension
» constricted pupils or rarely, dilated pupils
» bradycardia
» respiratory depression
» hypothermia
» generalized seizures

Other complications include:
» hyperglycaemia,
» glycosuria,
» mild increase in transaminases.

Patients usually regain consciousness within 24 hours.

Note: Amitraz poisoning can be confused with organophosphate poisoning; whilst amitraz causes central nervous system depression, bradycardia, miosis and respiratory depression, it does not cause excessive sweating and salivation, urinary and faecal incontinence or muscle fasciculation which are seen with organophosphate poisoning. Furthermore, organophosphate toxicity results in reduced serum pseudocholinesterase levels.

GENERAL MEASURES
» Decontamination of skin and clothes where applicable.
» Supportive and symptomatic treatment to maintain patent airway, adequate respiration and circulation.
» Mechanical ventilation may be needed in some cases.
» Keep patient warm.

MEDICINE TREATMENT
- Activated charcoal, once patient is stabilised.

For severe bradycardia: R00.1 + (T44.4 + X43.99/X63.99/Y13.99)
Manage with atropine - see Section 3.3.3: Heart block (second or third degree).

For seizures: R56.8 + (T44.4 + X43.99/X63.99/Y13.99)
Treat with benzodiazepines - see Section 14.5: Status epilepticus.
Note: Phenytoin should be avoided (due to potential cardiotoxicity).

LoE:IVb[lxviii]

19.18.2 ORGANOPHOSPHATE POISONING
T60.0 + (X48.99/X68.99/Y18.99)
* Notifiable condition.
Poisoning from all pesticides (i.e. agricultural stock remedies) is a notifiable medical condition. Please visit https://nicd.ac.za/nmc-overview/notification-process for further information.

DESCRIPTION
Absorption may occur through the skin, gastrointestinal tract if taken orally, or by inhalation.
Patients present with muscarinic and nicotinic manifestations of intoxication.
» Peripheral effects:
  – *Muscarinic overstimulation:* bradycardia, hypotension, salivation, lacrimation, vomiting, diarrhoea, increased bronchial secretions, bronchospasm, and miosis (pinpoint pupils).
  – *Nicotinic overstimulation:* muscle weakness and fasciculations, tachycardia, hypertension, mydriasis (dilated pupils).

» Central effects: coma, confusion, convulsions.

Diagnosis is supported by low serum pseudocholinesterase levels.

Intermediate syndrome can occur within 1 to 4 days after recovery from cholinergic crisis. Patients develop weakness or paralysis predominantly affecting the muscles of respiration (including the neck flexors and bulbar muscles) and proximal limb muscles, sparing the distal muscles. Cranial nerves may also be affected. Supportive care is the mainstay of therapy.

LoE:IIIa[lxix]

CAUTION

A history of an unspecified rat poison or pesticide exposure warrants consideration of other active ingredients such as super-warfarin anticoagulants and amitraz.

GENERAL MEASURES

» Ensure use of personal protective equipment for staff – gloves, gowns, and eye protection. If staff come into contact with body fluids, wash off immediately.

» Decontamination procedures for the patient should only be done once the patient is fully resuscitated. *LoE:IIIa*[lxx]

» Remove patient's clothes and wash the body with soap and water. Place clothes in closed bags.

» Maintain adequate ventilation and circulation. Ventilatory support in ICU may be required. Suction secretions frequently.

» Note: If using suxamethonium for intubation, consider that metabolism may be delayed and prolonged respiratory support may be required. Use alternative agents if possible. (See Section 12.3: Muscle relaxants).

MEDICINE TREATMENT

- Activated charcoal, once patient is stabilised.

For bronchorrhoea, bronchospasm, or bradycardia: *LoE:IIIa*[lxxi]

STEP 1:

- Atropine bolus, IV
  - Administer 2mg atropine as an IV bolus.
  - Reassess after 3–5 minutes for evidence of atropinisation as indicated by reduced bronchial secretions, dry skin, increasing heart rate and blood pressure, and dilating pupils (note: pupil dilatation may be delayed).
  - Give repeated atropine boluses incrementally doubling the dose until adequate clinical response achieved, e.g. 2 mg, 4 mg, 8 mg, 16 mg etc.
    - If no clinical response, give double the dose.
    - If some response, give the same or reduced dose.

ATROPINE : SECTION 21

A high strength formulation (100mg in 10mL) of atropine may be available at select facilities. Confirm the strength available before preparing and administering to the patient.

STEPS TO FOLLOW	**ATROPINE FORMULATIONS**		
Select formulation of atropine available	**100mg/10mL ampoule SECTION 21**	**1mg/mL ampoule**	**500mcg/mL ampoule**
Prepare atropine syringe for IV bolus	Dilute 1mL atropine with 9mL diluent for a 1mg/mL solution.	Use undiluted	
Atropine doses	**Volume of atropine**		
	Diluted 1mg/mL solution SECTION 21	**1mg/mL ampoule**	**500mcg/mL ampoule**
2mg	2mL	2mL	4mL
4mg	4mL	4mL	8mL
8mg	8mL	8mL	16mL
16mg	16mL	16mL	32mL
32mg	32mL	32mL	64mL
etc			
Total bolus dose = e.g. 62mg			

STEP 2:

- Atropine IV infusion
  - Calculate the total dose of atropine given as boluses. Give 10 to % of this dose per hour, titrating up to 20% per to hour based on clinical response. to

Worked example: Total bolus dose = 62mg. Administer 10-20% (6-12mg) per hour by IV infusion.			
STEPS TO FOLLOW	**ATROPINE FORMULATIONS**		
Select formulation of atropine available	**Atropine 100mg/10mL ampoule (SECTION 21)**	**Atropine 1mg/mL ampoule**	**Atropine 500mcg/mL ampoule**
Prepare solution for IV infusion	200mg atropine = 20mL (2 amps) Add to 180mL diluent to prepare a 1mg/mL atropine solution	40mg atropine = 40mL (40 amps) Add to 160mL diluent to prepare a	40mg atropine = 80mL (80 amps) Add to 120mL diluent to prepare a

		0.2mg/mL solution	0.2mg/mL solution
Calculate 10% of total bolus dose to be given per hour	6mg	6mg	6mg
Start infusion at rate equivalent to 10% of bolus dose	6mL/hour	30mL/hour	30mL/hour

- Titrate according to clinical response, by frequent reassessment and adjustments:
  - Bronchial secretions, bronchospasm or bradycardia recurs: increase dose.
  - Good control of bronchial secretions and signs of atropine overdose (tachycardia, mydriasis, agitation, pyrexia, reduced bowel sounds and urinary retention): decrease dose.
  - No recurrence of bronchial secretions and no signs of atropine overdose: reduce dose slowly.

STEP 3 (May be required in some patients)

- Atropine bolus, IV — *LoE:IVb*
  - Some organophosphates are lipophilic in nature and cholinergic symptoms may recur even once the atropine infusion is in place. In such cases, repeat bolus doses, starting at 2mg, can be given in addition to the atropine infusion. Bolus doses may be increased incrementally as in Step 1 above.
  - Once the patient is restabilised, consider increasing the infusion rate, to 10% of the new total bolus doses i.e.

Infusion rate = 0.1 X (STEP 1 total bolus dose + STEP 3 total bolus dose).

  - Titrate the infusion rate up to 20% based on clinical response.

Note:

» Do not stop atropine infusion abruptly; instead, wean over at least 24 hours.

» Tachycardia and mydriasis are not contraindications for giving atropine in the acute resuscitation setting.

LoE:IIIa[lxxii]

For severe agitation:

- Diazepam, IV, 5–10 mg, immediately.
  - Repeat after 30–60 minutes if needed.

LoE:IIIa[lxxiii]

REFERRAL

Refer if ventilatory support is unavailable.

19.18.3 PARAQUAT POISONING

T60.3 + (X48.99/X68.99/Y18.99)

* Notifiable condition.

Poisoning from all pesticides (i.e. agricultural stock remedies) is a notifiable medical condition. Please visit https://nicd.ac.za/nmc-overview/notification-process for further information.

DESCRIPTION

Paraquat is the most toxic herbicide known, and toxicity causes multi-organ failure which is often fatal. Following oral ingestion, patients present with oral, oesophageal, and gastric erosions with severe gastroenteritis. Multi-organ failure develops within 1 to 3 days, particularly renal and respiratory failure. Patients surviving the initial phase usually develop pulmonary fibrosis.

GENERAL MEASURES

» Supportive and symptomatic management to maintain patent airway, adequate respiration, and circulation.
» Mechanical ventilation may be needed in some cases.
» Palliative care is the mainstay of treatment.

CAUTION

High inspiratory fraction of inspired oxygen (FiO2) may worsen pulmonary toxicity. Supplemental oxygen should only be provided if the patient is confirmed hypoxic.

MEDICINE TREATMENT

- Activated charcoal

19.19 ANTICOAGULANT (WARFARIN AND RODENTICIDE SUPERWARFARIN) POISONING

T45.5 + (X44.99/X64.99/Y14.99)

* Notifiable condition – rodenticide superwarfarin poisoning

Poisoning from all pesticides (i.e. agricultural stock remedies) is a notifiable medical condition. Please visit https://www.nicd.ac.za/nmc-overview/notification-process/ further information.

DESCRIPTION

Poisoning due to ingestion of warfarin and superwarfarins, e.g. rat poison and other vermin poisons. Warfarin toxicity can occur with either acute overdose or unintentionally, during therapeutic use, whereby drug interactions increase warfarin bioavailability (e.g. concomitant enzyme inhibitor), or concomitant anticoagulant drugs are administered (e.g. NSAIDS). Bleeding is the main clinical presentation e.g. gastrointestinal or intracranial bleeding; however bleeding may be occult. Superwarfarins

are more potent than warfarin and may have a long duration of effect; small doses of concentrated formulations may cause significant anticoagulation.

CAUTION
Where the history is of an unspecified rat poison or pesticide ingestion, consider other active ingredients such as amitraz and organophosphates.

GENERAL MEASURES

» Resuscitation.
» Stop warfarin in patients on therapy.
» Measure INR at baseline and 48 hours post ingestion, as the anticoagulant effect may be delayed by 1 to 2 days.

MEDICINE TREATMENT

Do NOT give vitamin K_1 prophylactically. It is only indicated when there is active bleeding or a specifically raised INR (INR > 4).

Active bleeding:
R58 + (T45.5 + X44.99/X64.99/Y14.99)
- Lyophilised plasma, IV, 15 mL/kg.

OR *LoE:IIIa*[lxxiv]
- Fresh Frozen Plasma, IV, 15 mL/kg.

AND
- Vitamin K_1, IV, 10 mg
  - Administer as a slow IV injection.
  - Do not dilute or mix with other injectables.

For patients on long term vitamin K antagonist anticoagulants, e.g. warfarin:
  - Temporarily discontinue anticoagulant therapy.
  - Decrease Vitamin K dose by half, i.e. Vitamin K1, IV, 5 mg. Administer as a slow IV injection. *LoE:IV*

No bleeding but INR is raised (INR >4):
Note: If Vitamin K_1 is only available as a parenteral preparation, administer the same preparation orally as this is safest in anticoagulant poisoning.

Patients NOT on long-term therapeutic anticoagulants and INR >4.0:
- Vitamin K_1, oral, 10 to 20 mg.
  - Check INR at least 12 hours after vitamin K_1 has been administered. Repeated doses should be guided by further INR (or PT) measurements every 4 to 6 hours until the patient is stable, and thereafter, every 24 hours. INR (or PT) levels may take 3 to 4 days to normalise.

Patients on long-term vitamin K antagonist anticoagulant drugs (e.g. warfarin therapy):

If INR 5 to 8:

- Temporarily discontinue any anticoagulant treatment.

If INR >8:

- Vitamin K_1, oral, 0.5 to 1.0 mg (one tenth of the normal dose).
  - A repeat dose may be given 12 to 24 hrs later if the INR remains ≥8. *LoE:IVb*[lxxv]

Note:

» These patients are complex and require management in consultation with a haematologist.

» Patients with prosthetic heart valves receiving high-dose vitamin K have a higher risk for increased resistance to warfarin and development of thromboembolism. Treat as above but monitor INR frequently to prevent overcorrection. Treat in consultation with a specialist.

» For patients on other anticoagulant therapies, additional antagonists may be required.

» In all patients on therapeutic warfarin, a major overdose or bleeding episode should prompt careful review of the need for anticoagulation.

» Warfarin should be re-started once the INR is in the therapeutic range if it is still indicated.

» In patients with superwarfarin toxicity, treatment with vitamin K_1 may need to be prolonged for several months as superwarfarins are very long acting. Discuss with the Poisons Information Centre or haematologist for advice on dosing and duration of treatment.

19.20 CARBON MONOXIDE POISONING

T58 + (X47.99/X67.99/Y17.99)

DESCRIPTION

Poisoning caused by accidental or intentional exposure to fires in poorly ventilated areas, combustion engines, faulty stoves, and faulty heating systems.

Patients present with:

» dizziness
» headache
» seizures and other CNS symptoms
» nausea and vomiting
» metabolic acidosis (severe)
» high arterial carboxyhaemoglobin levels
» impaired level of consciousness
» tachycardia
» chest pain
» retinal haemorrhages
» respiratory alkalosis (mild)

Note: There may be a normal arterial PaO2, but low oxygen saturation on pulse oximetry. Neither are useful in assessing severity of carbon monoxide poisoning. Ideally, a blood gas sample should be sent for co-oximetry to specifically detect carboxyhaemoglobin levels.

GENERAL MEASURES

» Remove patient from toxic environment.
» Ventilation may be needed in deeply comatosed patients.
» Monitor ECG and neurological status.

MEDICINE TREATMENT

- Oxygen, 100%, via positive pressure facemask.

For seizures: R56.8 + (T58 + X47.99/X67.99/Y17.99)
Treat with benzodiazepines - see Section14.5: Status epilepticus.
Note: Phenytoin should be avoided (due to potential cardiotoxicity).

LoE:IVb[lxxvi]

Metabolic acidosis:
Metabolic acidosis shifts the oxygen-dissociation curve to the right and therefore aids in maintaining tissue oxygenation despite reduced haemoglobin carrying capacity. Metabolic acidosis should only be treated if profound and persistent, following standard treatment protocols.

Patients should be followed up after discharge for the persistence of neurocognitive symptoms.

19.21 HEAVY METAL POISONING

T56.0/T56.1/T56.4/T56.8/T57.0

DESCRIPTION

This includes mercury, arsenic, gold, copper, lead poisoning, thallium etc. Frequent/occupational inhalation of metal fumes and particles can cause metal fume fever, a flu-like syndrome with fever, malaise, bronchospasm, and bi-weekly variations in severity that may be mildest on the weekend and most severe on Monday or Tuesday after returning to work. This may be confused with an acute viral illness with fever, cough, sweating, myalgia, headache etc. The course of the illness is usually benign.

The management of heavy metal toxicity depends on the specific metal, route of exposure and length of time between exposure and clinical presentation of symptoms. Discuss all potential patients with the Poisons Information Helpline for further investigation, treatment options and possible referral.

LoE:IVb[lxxvii]

Metal	Signs and symptoms
Copper salts	GIT irritation, hepatotoxicity, and haemolysis.
Arsenic	Impairs cellular respiration, resulting in multi-organ dysfunction.
Mercury	Clinical effects depend on the route of exposure and type of mercury (inorganic versus organic).
Lead	Chronic toxicity more common. Affects nervous, gastrointestinal, renal, and haematopoietic systems.
Gold	Deposition of immune complexes in kidneys and skin; mucus membrane inflammation.
Thallium	Alopecia and painful ascending peripheral neuropathy.

Table 19.6: Clinical features of heavy metal poisoning

LoE:IVb[lxxviii]

19.22 POISONING WITH SUBSTANCES THAT CAUSE METHAEMOGLOBINAEMIA

D74.9 + (T41.3/T41.4/T46.3 + X44.99/X64.99/Y14.99)

DESCRIPTION

» Substances causing methaemoglobinaemia include nitrites, nitroglycerine, dapsone, mothballs (naphthalene), local anaesthetics, phenazopyridine, chlorates, and anilines.
» Nitrites are used to cure meat in the formal and informal butchery sector.
» Patients present with:
  – Deep cyanosis with only mildly reduced oxygen saturation
  – CNS depression, and
  – arrhythmias.

Note: Methaemoglobinaemia causes patients to appear cyanosed with falsely high conventional pulse oximetry readings and normal PaO2. Blood gas analysis using co-oximetry is required to specifically measure methaemoglobin levels.

MEDICINE TREATMENT

- Oxygen via facemask.

In symptomatic cases or patients with high methaemoglobin values > 30%:

- Methylene blue (methylthionine chloride) 1% dilute solution, slow IV infusion, 1 to 2 mg/kg administered over 5 minutes.
  - Repeat in 1 hour and, if necessary, 4 hourly up to a total dose of 7 mg/kg.
  - Side effects include precordial pain, restlessness, and dyspnoea.
  - After administration of methylene blue, oxygen saturation may drop initially.

In life-threatening cases not responding to methylene blue, or if methylene blue is not available, exchange transfusion may be considered. Refer to the Poisons Information Helpline for advice on treatment and possible alternatives to methylene blue.

References

[i] G.J. Muller, H. Modler, C.A. Wium, C.J. Marks and D.J.H. Veale; Snake bite in southern Africa: diagnosis and management. Published Online:1 Oct 2012. https://hdl.handle.net/10520/EJC126922
Hardcastle T, Engelbrecht A, Lalloo V, Bell C, Toubkin M. Approach to the diagnosis and management of snakebite envenomation in South Africa in humans. S Afr Med J. 2023 Jun 5;113(6):12-18. doi: 10.7196/SAMJ.2023.v113i6.1037. PMID: 37278261. https://samajournals.co.za/index.php/samj/article/view/1037/498

[ii] Amoxicillin/clavulanic acid, oral: Blaylock RS. Antibiotic use and infection in snakebite victims. S Afr Med J. 1999 Aug;89(8):874-6. http://www.ncbi.nlm.nih.gov/pubmed/10488365

[iii] NSAID caution: World Health Organisation: Guidelines for the prevention and clinical management of snakebite in Africa. https://www.who.int/health-topics/snakebite#tab=overview

[iv] Polyvalent antivenom: Wood D, Webb C, DeMeyer J. Severe snakebites in northern KwaZulu-Natal: treatment modalities and outcomes. S Afr Med J. 2009 Nov;99(11):814-8. http://www.ncbi.nlm.nih.gov/pubmed/20218483
Polyvalent antivenom: Müller GJ, Modler H, Wium CA, Veale DJH, Marks CJ. Snake bite in southern Africa: diagnosis and management. CME Oct 2012; 30(10):362-82.http://www.cmej.org.za/index.php/cmej/article/view/2546/2581
SAMF 14th edition, page 653

[v] Antivenom (period to administer): Müller GJ, Modler H, Wium CA, Veale DJH, Marks CJ. Snake bite in southern Africa: diagnosis and management. CME Oct 2012; 30(10):362-82. http://www.cmej.org.za/index.php/cmej/article/view/2546/2581

[vi] Polyvalent snake antivenom (indications): Wood D, Sartorius B, Hift R. Snakebite in NE South Africa: clinical characteristics and risks for severity. S Afr Fam Prac 2016; 58(2):62-67. https://www.tandfonline.com/doi/full/10.1080/20786190.2015.1120934
Polyvalent snake antivenom (indications): Wood, Sartorius, Hift. Classifying snakebite in South Africa: validating a scoring system. S Afr Med J 2017;107(1):46-51. https://www.ncbi.nlm.nih.gov/pubmed/28112091
Hardcastle TC et al (progressive cytotoxic envenomation) . Approach to the diagnosis and management of snakebite envenomation in South Africa in humans: The hospital phase – emergency unit general principles. SAMJ June 2023 Vol 113, No6.

[vii] Adrenaline (epinephrine), SC: Nuchpraryoon I, Garner P. Interventions for preventing reactions to snake antivenom. Cochrane Database Syst Rev. 2000;(2):CD002153. Review. http://www.ncbi.nlm.nih.gov/pubmed/21572992
Adrenaline (epinephrine), SC: de Silva HA, Pathmeswaran A, Ranasinha CD, Jayamanne S, Samarakoon SB, Hittharage A, Kalupahana R, Ratnatilaka GA, Uluwatthage W, Aronson JK, Armitage JM, Lalloo DG, de Silva HJ. Low-dose adrenaline, promethazine, and hydrocortisone in the prevention of acute adverse reactions to antivenom following snakebite: a randomised, double-blind, placebo-controlled trial. PLoS Med. 2011 May;8(5):e1000435. http://www.ncbi.nlm.nih.gov/pubmed/21572992

[viii] Polyvalent antivenom (neurotoxic, cytotoxic or unidentified snakebites): Müller GJ, Modler H, Wium CA, Veale DJH, Marks CJ. Snake bite in southern Africa: diagnosis and management. CME Oct 2012; 30(10):362-82.http://www.cmej.org.za/index.php/cmej/article/view/2546/2581
Polyvalent antivenom: South African Medicines Formulary. 14th Edition. Division of Clinical Pharmacology. University of Cape Town, 2022.

[ix] Polyvalent antivenom (cytotoxic Mozabique spitting cobra bite): World Health Organisation: Guidelines for the prevention and clinical management of snakebite in Africa. https://www.who.int/health-topics/snakebite#tab=overview

[x] Boomslang monovalent antivenom (neurotoxic, cytotoxic or unidentified snakebites): Müller GJ, Modler H, Wium CA, Veale DJH, Marks CJ. Snake bite in southern Africa: diagnosis and management. CME Oct 2012; 30(10):362-82. http://www.cmej.org.za/index.php/cmej/article/view/2546/2581
Boomslang monovalent antivenom: Guidelines for the prevention and clinical management of snakebite in Africa. https://www.who.int/health-topics/snakebite#tab=overview

[xi] Local anaesthetic ophthamlmic drops (therapeutic group): Lawrenson JG, Edgar DF, Tanna GK, Gudgeon AC. Comparison of the tolerability and efficacy of unit-dose, preservative-free topical ocular anaesthetics. Ophthalmic Physiol Opt. 1998 Sep;18(5):393-400. https://pubmed.ncbi.nlm.nih.gov/10023471/

[xii] Polyvalent antivenom (snake venom in the eye): Müller GJ, Modler H, Wium CA, Veale DJH, Marks CJ. Snake bite in southern Africa: diagnosis and management. CME Oct 2012; 30(10):362-82. http://www.cmej.org.za/index.php/cmej/article/view/2546/2581

[xiii] Scorpion sting in southern Africa : diagnosis and management: G.J. Muller, H. Modler, C.A. Wium, D.J.H. Veale. CME Oct 2012; 30(10):356-61 https://journals.co.za/doi/epdf/10.10520/EJC126923

[xiv] Paracetamol, oral: Müller GJ, Modler H, Wium CA, Veale DJH, Marks CJ. Scorpion sting in southern Africa: diagnosis and management. CME Oct 2012; 30(10):356-61.http://www.cmej.org.za/index.php/cmej/article/view/2545/2580

[xv] Lidocaine. 1-2%, infiltration:Aksel G, Güler S, Doğan N, Corbacioğlu S. A randomized trial comparing intravenous paracetamol, topical lidocaine, and ice application for treatment of pain associated with scorpion stings. Hum ExpToxicol. 2014 Oct 10. pii: 0960327114551394. [Epub ahead of print] http://www.ncbi.nlm.nih.gov/pubmed/25304965
Lidocaine. 1-2%, infiltration: Chippaux JP. Emerging options for the management of scorpion stings. Drug Des Devel Ther. 2012;6:165-73. http://www.ncbi.nlm.nih.gov/pubmed/22826633

[xvi] Opiates (caution): Müller GJ, Modler H, Wium CA, Veale DJH, Marks CJ. Scorpion sting in southern Africa: diagnosis and management. CME Oct 2012; 30(10):356-61. http://www.cmej.org.za/index.php/cmej/article/view/2545/2580

[xvii] Scorpion sting: Muller, G J et al. Scorpion sting in southern Africa: diagnosis and management. Continuing Medical Education, [S.l.], v. 30, n. 10, p. 356-361, sep. 2012. ISSN 2078-5143. Available at: <http://www.cmej.org.za/index.php/cmej/article/view/2545/2580>. Date accessed: 18 Apr. 2023.

[xviii] Calcium gluconate 10%, bolus IV: South African Medicines Formulary. 14th Edition. Division of Clinical Pharmacology. University of Cape Town, 2022.
Package Insert: Calcium Gluconate Injection Fresenius solution for injection. Fresenius Kabi Manufacturing SA (Pty) Ltd. Last revised 7 February 2023.
Shann F. Drug doses: 17th Edition. 2017.

[xix] Spider bite in southern Africa : diagnosis and management: G.J. Muller, C.A. Wium, C.J. Marks, C.E. du Plessis, and D.J.H. Veale. CME October 2012;30(10): 382-92. https://journals.co.za/doi/epdf/10.10520/EJC126921

[xx] Spider antivenom: Muller GJ, Wium CA, Marks CJ, du Plessis CE, Veale DJH. Spider bite in southern Africa: diagnosis and management. CME October 2012;30(10): 382-91. http://www.cmej.org.za/index.php/cmej/article/view/2547/2582

[xxi] Calcium gluconate 10%, bolus IV: South African Medicines Formulary. 14th Edition. Division of Clinical Pharmacology. University of Cape Town, 2022.
Package Insert: Calcium Gluconate Injection Fresenius solution for injection. Fresenius Kabi Manufacturing SA (Pty) Ltd. Last revised 7 February 2023.
Shann F. Drug doses: 17th Edition. 2017.

[xxii] Gastric lavage: Benson BE, Hoppu K, Troutman WG, Bedry R, Erdman A, Höjer J, Mégarbane B, Thanacoody R, Caravati EM; American Academy of Clinical Toxicology; European Association of Poisons Centres and Clinical Toxicologists. Position paper update: gastric lavage for gastrointestinal decontamination. Clin Toxicol (Phila). 2013 Mar;51(3):140-6. https://www.ncbi.nlm.nih.gov/pubmed/23418938

[xxiii] Activated charcoal (multi-dose): Position statement and practice guidelines on the use of multi-dose activated charcoal in the treatment of acute poisoning. American Academy of Clinical Toxicology; European Association of Poisons Centres and Clinical Toxicologists. J ToxicolClinToxicol. 1999;37(6):731-51.http://www.ncbi.nlm.nih.gov/pubmed/10584586

[xxiv] Activated charcoal (single dose): National Department of Health: Affordable Medicines, EDP-Adult Hospital level. Medicine Review: Single dose activated charcoal for poisonings, May 2019. http://www.health.gov.za/
Activated charcoal (single dose): Chyka PA, Seger D; American Academy of Clinical Toxicology; European Association of Poisons Centres and Clinical Toxicologists. Position statement: single-dose activated charcoal. J Toxicol Clin Toxicol 1997;35(7):721-41. https://www.ncbi.nlm.nih.gov/pubmed/15822758
Activated charcoal (single dose): Rosenberg J, Benowitz NL, Pond S. Pharmacokinetics of drug overdose. Clin Pharmacokinet 1981; 6:161– 192. https://www.ncbi.nlm.nih.gov/pubmed/7016383
Activated charcoal (single dose): Yeates PJA, Thomas SHL. Effectiveness of delayed activated charcoal administration in simulated paracetamol (acetaminophen) overdose. Br J Clin Pharmacol 2000; 49:11–14. https://www.ncbi.nlm.nih.gov/pubmed/7016383
Activated charcoal (single dose): Laine K, Kivisto¨ KT, Pelttari S, Neuvonen PJ. The effect of activated charcoal on the absorption of fluoxetine, with special reference to delayed charcoal administration. Pharmacol Toxicol 1996; 79:270– 273. https://www.ncbi.nlm.nih.gov/pubmed/8936562
Activated charcoal (single dose): Laine K, Kivisto¨ KT, Neuvonen PJ. Effect of delayed administration of activated charcoal on the absorption of conventional and slow-release verapamil. J Toxicol Clin Toxicol 1997; 35:263–268. https://www.ncbi.nlm.nih.gov/pubmed/9140320
Activated charcoal (single dose): Laine K, Kivisto¨ KT, Ojala-Karlsson P, Neuvonen PJ. Effect of activated charcoal on the pharmacokinetics of pholcodine, with special reference to delayed charcoal ingestion. Ther Drug Monit 1997; 19:46– 50. https://www.ncbi.nlm.nih.gov/pubmed/9029746
Activated charcoal (single dose): Green R, Grierson R, Sitar DS, Tenenbein M. How long after drug ingestion is activated charcoal still effective? J Toxicol Clin Toxicol 2001; 39:601– 605. https://www.ncbi.nlm.nih.gov/pubmed/11762668

[xxv] Whole bowel irrigation (with polyethylene glycol): Thanacoody R, Caravati EM, Troutman B, Hojer J, Benson B, Hoppu K et al. Position paper update: whole bowel irrigation for gastrointestinal decontamination of overdose patients. Clin Toxicol (Phila) 2015;53:5-12. https://www.ncbi.nlm.nih.gov/pubmed/25511637

[xxvi] Paracetamol overdosing – repeated subtherapeutic ingestion: Chiew AL, Reith D, Pomerleau A, Wong A, Isoardi KZ, Soderstrom J, Buckley NA. Updated guidelines for the management of paracetamol poisoning in Australia and New Zealand. Med J Aust. 2020 Mar;212(4):175-183. https://pubmed.ncbi.nlm.nih.gov/31786822/

[xxvii] Paracetamol nomogram: Chiew AL, Reith D, Pomerleau A, Wong A, Isoardi KZ, Soderstrom J, Buckley NA. Updated guidelines for the management of paracetamol poisoning in Australia and New Zealand. Med J Aust. 2020 Mar;212(4):175-183. https://pubmed.ncbi.nlm.nih.gov/31786822/
Paracetamol nomogram: Daly FF, Fountain JS, Murray L, Graudins A, Buckley NA; Panel of Australian and New Zealand clinical toxicologists. Guidelines for the management of paracetamol poisoning in Australia and New Zealand - -explanation and elaboration. A consensus statement from clinical toxicologists consulting to the Australasian poisons information centres. Med J Aust. 2008 Mar 3;188(5):296-301.http://www.ncbi.nlm.nih.gov/pubmed/18312195

[xxviii] N-Acetycysteine,IV (dosing regimen): Chiew AL, Reith D, Pomerleau A, Wong A, Isoardi KZ, Soderstrom J, Buckley NA. Updated guidelines for the management of paracetamol poisoning in Australia and New Zealand. Med J Aust. 2020 Mar;212(4):175-183. https://pubmed.ncbi.nlm.nih.gov/31786822/
N-Acetycysteine,IV (dosing regimen): Wong A, Graudins A. Simplification of the standard three-bag intravenous acetylcysteine regimen for paracetamol poisoning results in a lower incidence of adverse drug reactions. Clin Toxicol (Phila). 2016;54(2):115-9. https://www.ncbi.nlm.nih.gov/pubmed/26594846

[xxix] N-acetylcysteine, oral (dosing for paracetamol poisoning): Yarema MC, Johnson DW, Berlin RJ, Sivilotti ML, Nettel-Aguirre A, Brant RF, et al. Comparison of the 20-hour intravenous and 72-hour oral acetylcysteine protocols for the treatment of acute acetaminophen poisoning. Ann Emerg Med. 2009 Oct;54(4):606-14. https://www.ncbi.nlm.nih.gov/pubmed/19556028
N-acetylcysteine, oral (dosing for paracetamol poisoning): Williamson K, Wahl MS, Mycyk MB. Direct comparison of 20-hour IV, 36-hour oral, and 72-hour oral acetylcysteine for treatment of acute acetaminophen poisoning. Am J Ther. 2013 Jan;20(1):37-40. https://www.ncbi.nlm.nih.gov/pubmed/23299230
N-acetylcysteine, oral (dosing for paracetamol poisoning): Rumack and Bateman. Acetaminophen and acetylcysteine dose and duration: past, present and future. Clin Toxicol (Phila) 2012;50(2):91-98. https://www.ncbi.nlm.nih.gov/pubmed/22320209

[xxx] N-acetylcysteine, oral (adverse effects): South African Medicines Formulary. 14th Edition. Division of Clinical Pharmacology. University of Cape Town, 2022.

[xxxi] Activated charcoal:Bradberry SM, Vale JA. Multiple-dose activated charcoal: a review of relevant clinical studies. J ToxicolClinToxicol. 1995;33(5):407-16. Review. http://www.ncbi.nlm.nih.gov/pubmed/7650765
Whole bowel irrigation:Mayer AL, Sitar DS, Tenenbein M. Multiple-dose charcoal and whole-bowel irrigation do not increase clearance of absorbed salicylate. Arch Intern Med. 1992 Feb;152(2):393-6. http://www.ncbi.nlm.nih.gov/pubmed/1739372

[xxxii] Activated charcoal:Bradberry SM, Vale JA. Multiple-dose activated charcoal: a review of relevant clinical studies. J ToxicolClinToxicol. 1995;33(5):407-16. Review.http://www.ncbi.nlm.nih.gov/pubmed/7650765
Whole bowel irrigation:Mayer AL, Sitar DS, Tenenbein M. Multiple-dose charcoal and whole-bowel irrigation do not increase clearance of absorbed salicylate. Arch Intern Med. 1992 Feb;152(2):393-6. http://www.ncbi.nlm.nih.gov/pubmed/1739372

[xxxiii] Dextrose (salicylate poisoning): Kuzak N, Brubacher JR, Kennedy JR. Reversal of salicylate-induced euglycemic delirium with dextrose. Clin Toxicol (Phila). 2007 Jun-Aug;45(5):526-9. https://pubmed.ncbi.nlm.nih.gov/17503260/

[xxxiv] Sodium bicarbonate (salicylate poisoning): Prescott LF, Balali-Mood M, Critchley JA, Johnstone AF, Proudfoot AT. Diuresis or urinary alkalinisation for salicylate poisoning? Br Med J (Clin Res Ed). 1982 Nov 13;285(6352):1383-6. https://pubmed.ncbi.nlm.nih.gov/6291695/

[xxxv] Haemodialysis (salicylate poisoning): McCabe DJ, Lu JJ. The association of hemodialysis and survival in intubated salicylate-poisoned patients. Am J Emerg Med. 2017 Apr 10. pii: S0735-6757(17)30280-2. https://www.ncbi.nlm.nih.gov/pubmed/28438446
Haemodialysis (salicylate poisoning): Juurlink DN, Gosselin S, Kielstein JT, Ghannoum M, Lavergne V, Nolin TD, Hoffman RS; EXTRIP Workgroup. Extracorporeal Treatment for Salicylate Poisoning: Systematic Review and Recommendations From the EXTRIP Workgroup. Ann Emerg Med. 2015 Aug;66(2):165-81. https://pubmed.ncbi.nlm.nih.gov/25986310/

[xxxvi] Naloxone: South African Medicines Formulary. 14th Edition. Division of Clinical Pharmacology. University of Cape Town, 2022.
Naloxone: FDA approved package insert – Hospira Inc.: Naloxone Hydrochloride, 2015. http://medlibrary.org/lib/rx/meds/naloxone-hydrochloride-8/

[xxxvii] TCAs - toxicity: David M. Taylor, Thomas R. E. Barnes, Allan H. Young. The Maudsley prescribing guidelines in psychiatry.13th edition. Hoboken, NJ : Wiley, 2019. (page 770).

[xxxviii] Sodium bicarbonate, IV (tricyclic antidepressant poisoning): Bruccoleri RE, Burns MM. A Literature Review of the Use of Sodium Bicarbonate for the Treatment of QRS Widening. J Med Toxicol. 2016 Mar;12(1):121-9. https://www.ncbi.nlm.nih.gov/pubmed/26159649

[xxxix] Phenytoin (tricyclic antidepressant poisoning): South African Medicines Formulary. 14th Edition. Division of Clinical Pharmacology. University of Cape Town, 2022.

[xl] Flumazenil (tricyclic antidepressant poisoning): Penninga EI, Graudal N, Ladekarl MB, Jürgens G. Adverse Events Associated with Flumazenil Treatment for the Management of Suspected Benzodiazepine Intoxication - A Systematic

Review with Meta-Analyses of Randomised Trials. Basic ClinPharmacolToxicol. 2016 Jan;118(1):37-44. http://www.ncbi.nlm.nih.gov/pubmed/26096314

[xli] Desferrioxamine, IV: Tenenbein M. Benefits of parenteral deferoxamine for acute iron poisoning. J ToxicolClinToxicol. 1996;34(5):485-9. http://www.ncbi.nlm.nih.gov/pubmed/8800185

Desferrioxamine, IV: Tenenbein M, Kowalski S, Sienko A, Bowden DH, Adamson IY. Pulmonary toxic effects of continuous desferrioxamine administration in acute iron poisoning. Lancet. 1992 Mar 21;339(8795):699-701. http://www.ncbi.nlm.nih.gov/pubmed/1347583

Desferrioxamine, IV: South African Medicines Formulary. 14th Edition. Division of Clinical Pharmacology. University of Cape Town, 2022.

[xlii] Deferoxamine (IV admin) Drug Monograph. Deferoxamine. Clinical Key accessed 3 February 2023. https://www.clinicalkey.com/#!/content/6-s2.0-170?scrollTo=%23top

Package Insert. Desferal. Novartis 10 Aug 2006.

[xliii]Desferrioxamine, IV (pregnancy): Piccioni MG, Capone C, Vena F, Del Negro V, Schiavi MC, D'Ambrosio V, Giancotti A, Smacchia MP, Brunelli R. Use of deferoxamine (DFO) in transfusion-dependent β-thalassemia during pregnancy: A retrospective study. Taiwan J Obstet Gynecol. 2020 Jan;59(1):120-122. https://pubmed.ncbi.nlm.nih.gov/32039778/

[xliv]Activated charcoal (multi-dose): Ghannoum M, Wiegand TJ, Liu KD, Calello DP, Godin M, Lavergne V, Gosselin S, Nolin TD, Hoffman RS; EXTRIP workgroup. Extracorporeal treatment for theophylline poisoning: systematic review and recommendations from the EXTRIP workgroup. Clin Toxicol (Phila). 2015 May;53(4):215-29. https://www.ncbi.nlm.nih.gov/pubmed/25715736

[xlv]Potassium chloride, IV: Ghannoum M, Wiegand TJ, Liu KD, Calello DP, Godin M, Lavergne V, Gosselin S, Nolin TD, Hoffman RS; EXTRIP workgroup. Extracorporeal treatment for theophylline poisoning: systematic review and recommendations from the EXTRIP workgroup. Clin Toxicol (Phila). 2015 May;53(4):215-29. https://www.ncbi.nlm.nih.gov/pubmed/25715736

[xlvi] Phenytoin (seizures secondary to poisonings): South African Medicines Formulary. 14th Edition. Division of Clinical Pharmacology. University of Cape Town, 2022.

[xlvii] Haemodialysis: Activated charcoal (multi-dose): Ghannoum M, Wiegand TJ, Liu KD, Calello DP, Godin M, Lavergne V, Gosselin S, Nolin TD, Hoffman RS; EXTRIP workgroup. Extracorporeal treatment for theophylline poisoning: systematic review and recommendations from the EXTRIP workgroup. Clin Toxicol (Phila). 2015 May;53(4):215-29. https://www.ncbi.nlm.nih.gov/pubmed/25715736

[xlviii] Flumazenil: Penninga EI, Graudal N, Ladekarl MB, Jürgens G. Adverse Events Associated with Flumazenil Treatment for the Management of Suspected Benzodiazepine Intoxication - A Systematic Review with Meta-Analyses of Randomised Trials. Basic ClinPharmacolToxicol. 2016 Jan;118(1):37-44.http://www.ncbi.nlm.nih.gov/pubmed/26096314

[xlix]Whole bowel irrigation (with polyethylene glycol): Thanacoody R, Caravati EM, Troutman B, Hojer J, Benson B, Hoppu K et al. Position paper update: whole bowel irrigation for gastrointestinal decontamination of overdose patients. Clin Toxicol (Phila) 2015;53:5-12. https://www.ncbi.nlm.nih.gov/pubmed/25511637

[l] Phenytoin (seizures secondary to poisonings): South African Medicines Formulary. 12th Edition. Division of Clinical Pharmacology. University of Cape Town, 2022.

[li] Haemodialysis (early referral): Decker BS, Goldfarb DS, Dargan PI, Friesen M, Gosselin S, Hoffman RS, Lavergne V, Nolin TD, Ghannoum M; EXTRIP Workgroup. Extracorporeal Treatment for Lithium Poisoning: Systematic Review and Recommendations from the EXTRIP Workgroup. Clin J Am Soc Nephrol. 2015 May 7;10(5):875-87. https://www.ncbi.nlm.nih.gov/pubmed/25583292

[lii]Pyridoxine, oral: Lheureux P, Penaloza A, Gris M. Pyridoxine in clinical toxicology: a review. Eur J Emerg Med. 2005 Apr;12(2):78-85. http://www.ncbi.nlm.nih.gov/pubmed/15756083

Pyridoxine, oral: Dilrukshi M, Ratnayake C, Gnanathasan C. Oral pyridoxine can substitute for intravenous pyridoxine in managing patients with severe poisoning with isoniazid and rifampicin fixed dose combination tablets: a case report. BMC Res Notes 2017;10:370. https://www.ncbi.nlm.nih.gov/pubmed/28789699

[liii] Benzodiazepines (seizures in INH toxicity): Hoffman RS, Howlands MA, Lewin Na, Nelson LS, Goldfrank LR. Goldfrank's Toxicologic Emergencies. 10th ed. China: McGraw-Hill Education; 2015.

[liv] Phenytoin (avoid in isoniazid poisoning): Hoffman RS, Howlands MA, Lewin Na, Nelson LS, Goldfrank LR. Goldfrank's Toxicologic Emergencies. 10th ed. China: McGraw-Hill Education; 2015.

[lv]Calcium channel blocker poisonings and beta-blocker poisonings (similar management): Graudins A, Lee HM, Druda D. Calcium channel antagonist and beta-blocker overdose: antidotes and adjunct therapies. Br J Clin Pharmacol. 2016 Mar;81(3):453-61. https://www.ncbi.nlm.nih.gov/pubmed/26344579

[lvi]Gut decontamination (Gastric lavage, activated charcoal administration or whole bowel irrigation): St-Onge M, Anseeuw K, Cantrell FL, Gilchrist IC, Hantson P, Bailey B, Lavergne V, Gosselin S, Kerns W 2nd, Laliberté M, Lavonas EJ, Juurlink DN, Muscedere J, Yang CC, Sinuff T, Rieder M, Mégarbane B. Experts Consensus Recommendations for the Management of Calcium Channel Blocker Poisoning in Adults. Crit Care Med. 2017 Mar;45(3):e306-e315. https://www.ncbi.nlm.nih.gov/pubmed/27749343

[lvii]Atropine, IV: Proano L, Chiang WK, Wang RY. Calcium channel blocker overdose. Am J Emerg Med. 1995

Jul;13(4):444-50. http://www.ncbi.nlm.nih.gov/pubmed/7605536

[lviii]Sodium chloride, 0.9%, IV: Proano L, Chiang WK, Wang RY. Calcium channel blocker overdose. Am J Emerg Med. 1995 Jul;13(4):444-50.http://www.ncbi.nlm.nih.gov/pubmed/7605536

[lix]Calcium gluconate 10%, IV (calcium channel blocker toxicity): Proano L, Chiang WK, Wang RY. Calcium channel blocker overdose. Am J Emerg Med. 1995 Jul;13(4):444-50. http://www.ncbi.nlm.nih.gov/pubmed/7605536

Calcium gluconate 10%, IV (calcium channel blocker toxicity): Graudins A, Lee HM, Druda D. Calcium channel antagonist and beta-blocker overdose: antidotes and adjunct therapies. Br J Clin Pharmacol. 2016 Mar;81(3):453-61. https://www.ncbi.nlm.nih.gov/pubmed/26344579

[lx] Phenytoin (seizures secondary to poisonings): South African Medicines Formulary. 14th Edition. Division of Clinical Pharmacology. University of Cape Town, 2022.

[lxi] Phenytoin (seizures secondary to poisonings): South African Medicines Formulary. 14th Edition. Division of Clinical Pharmacology. University of Cape Town, 2022.

[lxii] Endoscopic evaluation (within 24-48 hours): Millar AJ, Cox SG. Caustic injury of the oesophagus. Pediatr Surg Int. 2015 Feb;31(2):111-21. https://www.ncbi.nlm.nih.gov/pubmed/25432099

[lxiii] Ethanol (indications for antidote): McMartin K, Jacobsen D, Hovda KE. Antidotes for poisoning by alcohols that form toxic metabolites. Br J Clin Pharmacol. 2016 Mar;81(3):505-15. https://www.ncbi.nlm.nih.gov/pubmed/26551875

[lxiv] Ethanol (dosing of antidote): McMartin K, Jacobsen D, Hovda KE. Antidotes for poisoning by alcohols that form toxic metabolites. Br J Clin Pharmacol. 2016 Mar;81(3):505-15. https://www.ncbi.nlm.nih.gov/pubmed/26551875

[lxv] Co-factor therapy (ethylene glycol poisoning): Frommer JP, Ayus JC. Acute ethylene glycol intoxication. Am J Nephrol. 1982;2(1):1-5. https://pubmed.ncbi.nlm.nih.gov/7180899/

[lxvi] Metabolic acidosis cautions: McMartin K, Jacobsen D, Hovda KE. Antidotes for poisoning by alcohols that form toxic metabolites. Br J Clin Pharmacol. 2016 Mar;81(3):505-15. https://www.ncbi.nlm.nih.gov/pubmed/26551875

[lxvii] Ethanol antidote and haemodialysis (methanol poisoning): Jacobsen D, McMartin KE. Antidotes for methanol and ethylene glycol poisoning. J Toxicol Clin Toxicol. 1997;35(2):127-43. https://www.ncbi.nlm.nih.gov/pubmed/9120880

Ethanol antidote and haemodialysis (methanol poisoning): Roberts DM, Yates C, Megarbane B, Winchester JF, Maclaren R, Gosselin S, Nolin TD, Lavergne V, Hoffman RS, Ghannoum M; EXTRIP Work Group. Recommendations for the role of extracorporeal treatments in the management of acute methanol poisoning: a systematic review and consensus statement. Crit Care Med. 2015 Feb;43(2):461-72. https://www.ncbi.nlm.nih.gov/pubmed/25493973

[lxviii] Phenytoin (seizures secondary to poisonings): South African Medicines Formulary. 14th Edition. Division of Clinical Pharmacology. University of Cape Town, 2022.

[lxix] Intermediate syndrome in organophosphate poisoning: Eddleston M, Buckley NA, Eyer P, Dawson AH. Management of acute organophosphorus pesticide poisoning. Lancet. 2008 Feb 16;371(9612):597-607. https://www.ncbi.nlm.nih.gov/pubmed/17706760

[lxx] Organophosphate poisoning – healthcare worker protection: Little M, Murray L; Poison Information Centres of New South Wales, Western Australia, Queensland, New Zealand, and the Australian Capital Territory. Consensus statement: risk of nosocomial organophosphate poisoning in emergency departments. Emerg Med Australas. 2004 Oct-Dec;16(5-6):456-8. https://www.ncbi.nlm.nih.gov/pubmed/15537409

Organophosphate poisoning – healthcare worker protection: Centers for Disease Control and Prevention (CDC). Nosocomial poisoning associated with emergency department treatment of organophosphate toxicity--Georgia, 2000. MMWR Morb Mortal Wkly Rep. 2001 Jan 5;49(51-52):1156-8. https://www.ncbi.nlm.nih.gov/pubmed/11198947

Organophosphate poisoning – healthcare worker protection: Stacey R, Morfey D, Payne S. Secondary contamination in organophosphate poisoning: analysis of an incident. QJM. 2004 Feb;97(2):75-80. https://www.ncbi.nlm.nih.gov/pubmed/14747621

[lxxi] Atropine, IV (bolus dose): Abedin MJ, Sayeed AA, Basher A, Maude RJ, Hoque G, Faiz MA. Open-label randomized clinical trial of atropine bolus injection versus incremental boluses plus infusion for organophosphate poisoning in Bangladesh. J Med Toxicol. 2012 Jun;8(2):108-17. http://www.ncbi.nlm.nih.gov/pubmed/22351300

[lxxii] Atropine, IV (protocol): Eddleston M, Buckley NA, Eyer P, Dawson AH. Management of acute organophosphorus pesticide poisoning. Lancet. 2008 Feb 16;371(9612):597-607. https://www.ncbi.nlm.nih.gov/pubmed/17706760

Atropine, IV (protocol): Eddleston M, Dawson A, Karalliedde L, Dissanayake W, Hittarage A, Azher S, Buckley NA. Early management after self-poisoning with an organophosphorus or carbamate pesticide - a treatment protocol for junior doctors. Crit Care. 2004 Dec;8(6):R391-7. https://www.ncbi.nlm.nih.gov/pubmed/15566582

[lxxiii] Diazepam, IV (seizures in organophosphate poisoning): Eddleston M, Buckley NA, Eyer P, Dawson AH. Management of acute organophosphorus pesticide poisoning. Lancet. 2008 Feb 16;371(9612):597-607. https://www.ncbi.nlm.nih.gov/pubmed/17706760

[lxxiv]Freshfrozen plasma: Ansell J, Hirsh J, Hylek E, Jacobson A, Crowther M, Palareti G; American College of Chest Physicians. Pharmacology and management of the vitamin K antagonists: American College of Chest Physicians

Evidence-Based Clinical Practice Guidelines (8th Edition). Chest. 2008 Jun;133(6 Suppl):160S-198S.http://www.ncbi.nlm.nih.gov/pubmed/18574265

[lxxv] Watt BE et al. Anticoagulant rodenticides. Toxicol Rev 2005:24(4); 259-269

Toxinz and Toxbase – June 2022 printouts

Oxford Desk Reference Toxicology 2014 p311-312.

Goldfrank Toxicologic Emergencies 10th ed. P820 and 836-838.

[lxxvi] Phenytoin (seizures secondary to poisonings): South African Medicines Formulary. 14th Edition. Division of Clinical Pharmacology. University of Cape Town, 2022.

[lxxvii]Heavy metal poisoning (flu-like syndrome): Brenner BE, Keyes D. Metal Fume Fever. [Updated 2023 Aug 21]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2024 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK583199/.

Nelson LS, Odujebe OA. Simple Asphyxiants and Pulmonary Irritants. In: Nelson LS, Howland M, Lewin NA, Smith SW, Goldfrank LR, Hoffman RS. eds. Goldfrank's Toxicologic Emergencies, 11e. McGraw-Hill Education; 2019. Accessed April 16,

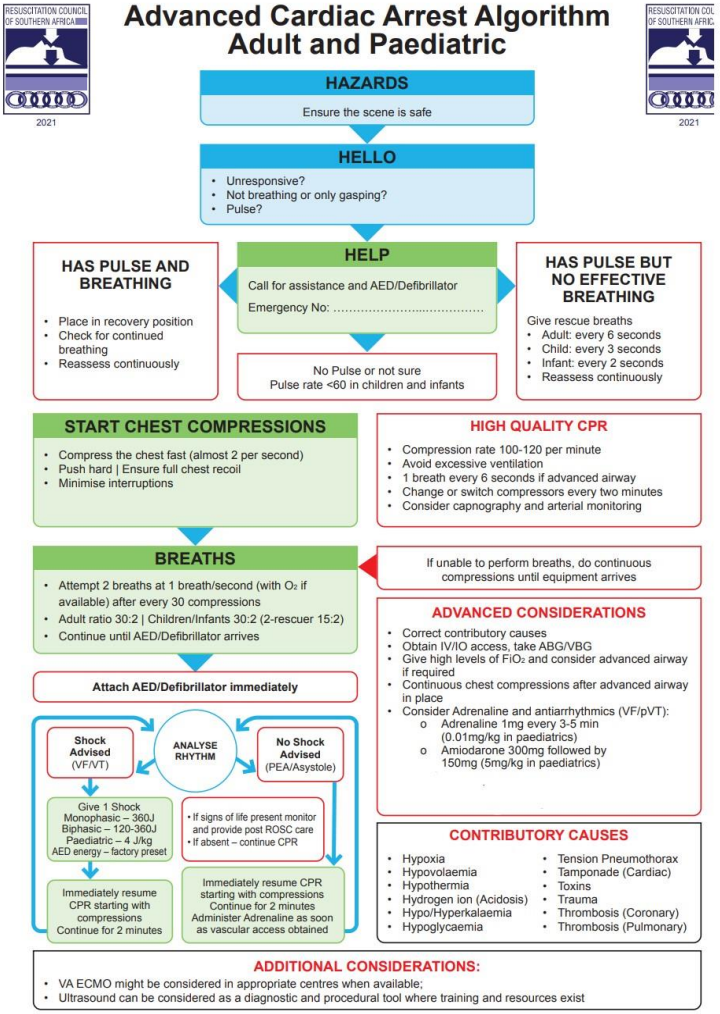
2024. https://accesspharmacy.mhmedical.com/content.aspx?bookid=2569&sectionid=210264279

https://www.msdmanuals.com/professional/special-subjects/occupational-and-environmental-medicine/metal-fume-fever-and-polymer-fume-fever?query=metal%20fume%20fever%20and%20polymer%20fume%20fever

[lxxviii]Heavy metal poisoning (signs and symptoms): AfriTox 2019. [Accessed September 2019]. www.afritox.co.za

CHAPTER 20
EMERGENCIES AND INJURIES

CARDIOPULMONARY RESUSCITATION



Abbreviations: CPR = Cardiopulmonary Resuscitation; PEA = Pulseless Electrical Activity; VF = Ventricular Fibrillation; VT = Ventricular Tachycardia.

Figure 20.1: Advanced cardiac arrest algorithm *(adapted with permission from the Resuscitation Council of South Africa)*

In context of COVID:

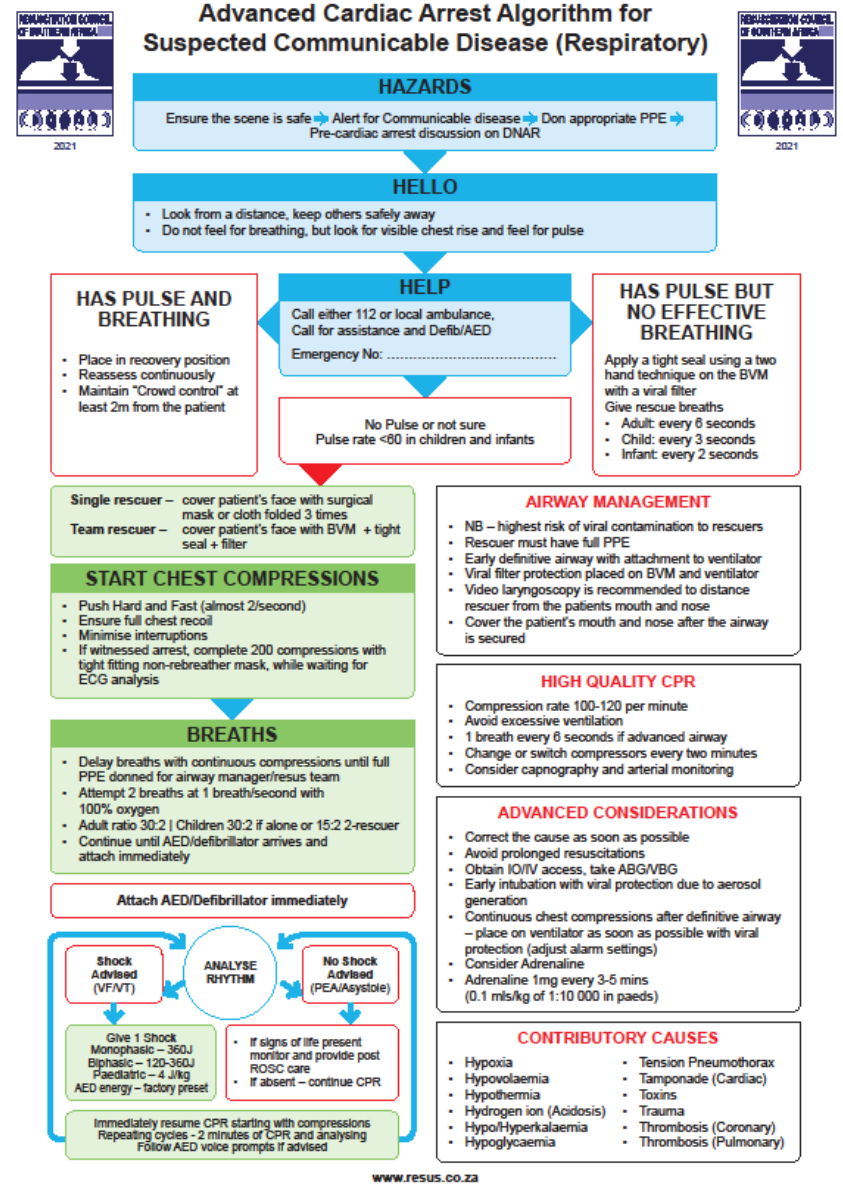


Figure 20.2: Advanced cardiac arrest algorithm - suspected respiratory communicable disease *(adapted with permission from the Resuscitation Council of South Africa)*

20.1 CARDIAC ARREST IN ADULTS

I46.0/I46.9

DESCRIPTION

Described as the loss of a heartbeat and a palpable pulse, irrespective of the electrical activity captured on ECG tracing. Irreversible brain damage can occur within 2–4 minutes.

Clinical features include:

» sudden loss of consciousness, absent carotid pulses
» loss of spontaneous respiration

LoE: IVb[i]

COVID-19 CONSIDERATIONS

» The infection risk that CPR poses to providers due to aerosolization of coronavirus particles is not negligible.
» This potential risk should be weighed against the probability of achieving spontaneous return of circulation to inform the decision to initiate or stop CPR.
» For in-hospital cardiac arrest in patients with suspected COVID-19, CPR has been shown to not be beneficial unless an immediate reversible cause is suspected, e.g., dislodgement of ET tube, etc. and is therefore not recommended.
» For out of hospital cardiac arrest in patients with suspected COVID-19, it is recommended to not start conventional CPR in unwitnessed cardiac arrest as it will likely not be beneficial.
» Appropriate PPE should be worn by all staff before initiating CPR: FFP3 mask, visor, gloves and gown.

LoE: IIIb[ii]

EMERGENCY TREATMENT

» Diagnose rapidly. After ensuring the safety of the scene, commence resuscitation as per the appropriate acute adult cardiac arrest algorithm – Fig 20.1 or 20.2 above.
» Make a note of the time of starting resuscitation.
» Place the patient on a firm flat surface and commence resuscitation immediately.
» Call for skilled help and an automated external defibrillator (AED) or defibrillator.
» Initiate CAB (Circulation Airway Breathing) sequence of CPR (cardiopulmonary resuscitation).
» Check the rhythm as soon as defibrillator or AED is available and defibrillate if a shockable rhythm is identified.
» Document medication and progress after the resuscitation.

Cardiopulmonary resuscitation (CPR)

Circulation

» Check for carotid pulse for about 5 seconds.
» If there is no pulse or you are not sure, start with chest compressions at a rate of 100-120 compressions per minute to a depth of +/- 5cm. Push hard

and allow full recoil of chest with minimum interruptions.

Airway and breathing

» To open the airway, lift the chin forward with the fingers of the one hand and tilt the head backwards with other hand on the forehead.
» **Note:** Do not do this where a neck injury is suspected – refer below for management of suspected neck injury.
» Ensure airway is open throughout resuscitation.
» If there is no normal breathing, attempt 2 respirations with bag-valve-mask resuscitator and face mask.
» The administered breaths must cause visible chest rising in patient. If not, reposition and try again once and proceed to next step.
» Repeat the cycle of 30 compressions followed by 2 respirations for 5 cycles and then re-assess for a pulse.
» If advanced airway is placed, administer 1 breath every 6 seconds without interrupting chest compressions. Avoid excessive ventilation.
• Oxygenate with 100% oxygen.
» Where neck injury is suspected:
  ✓ Do not perform a chin lift or head tilt manoeuvre if a neck injury is suspected.
  ✓ To open the airway, place your fingers behind the jaw on each side.
  ✓ Lift the jaw upwards while opening the mouth with your thumbs (jaw thrust).
  ✓ Maintain in line cervical spine immobilisation.

Initiate fluids, IV/IO access

• Sodium chloride 0.9%, IV — *LoE: IIb[iii]*
  o Administer a bolus of 1 litre during CPR if an increase in preload may benefit the patient, e.g., hypovolaemic shock, distributive shock, haemorrhagic shock.
  o Administer fluid cautiously during CPR if an increase in the preload could be detrimental, e.g., massive pulmonary embolism or cardiac tamponade. *LoE:IIIb[iv]*

If pulseless with shockable rhythm (ventricular fibrillation/tachycardia)

» Defibrillate, as indicated per algorithm.
» Immediately resume CPR, starting with chest compression.
» Continue CPR for 2 minutes.
• Administer adrenaline (epinephrine) as per algorithm and directions below (Immediate emergency medicine treatment).
» Seek reversible cause of arrest.
» Continue CPR until spontaneous breathing and/or pulse returns.
» For management of ventricular fibrillation or pulseless ventricular tachycardia that is unresponsive to defibrillation:
• Amiodarone, IV bolus, 300 mg, 2 minutes after adrenaline (epinephrine) dose.
  o Follow by a bolus of 10 mL sterile water or sodium chloride 0.9%.

- Patient remains in a shockable rhythm following further 2 minutes of CPR, a defibrillation shock, another adrenaline (epinephrine) dose, and another 2 minutes of CPR (5 cycles of 30:2): Amiodarone, IV bolus, 150 mg.

LoE:IIb[v]

If pulseless with non-shockable rhythm
» Immediately resume CPR. Starting with chest compression.
» Continue CPR for 2 minutes.
  - Administer adrenaline as per algorithm.
» Seek reversible cause of arrest.
» Continue CPR until spontaneous breathing and/or pulse returns.

Immediate emergency medicine treatment
Adrenaline (epinephrine) is the mainstay of treatment and should be given immediately, IV or intra-osseous, when there is no response to initial resuscitation or defibrillation.
- Adrenaline (epinephrine), 1:1 000, 1 mL, IV immediately, as a single dose.
  - Flush with 5–10 mL IV of sterile water or sodium chloride 0.9%.
  - Repeat every 3–5 minutes during resuscitation.

If no IV line is available:
- Adrenaline (epinephrine), intra-osseous (IO), 1:1000, 1 mL, via IO line. LoE:IVb[vi]
  - Flush with 5–10 mL of sterile water or sodium chloride 0.9%.
  - Repeat every 3–5 minutes during resuscitation.

ADDITIONAL GUIDANCE
Continue CPR until spontaneous breathing and/or heart beat returns.
Assess continuously (every 2 minutes) until the patient shows signs of recovery.

Termination of resuscitation:
» The decision to stop CPR attempts depends on the specifics of the individual patient and should be based on clinical judgement.
» Consider stopping resuscitation attempts and pronouncing death if there is incurable underlying disease, or if asystole > 20 minutes (in the absence of the factors below).

LoE: IIIb[vii]

Consider carrying on for longer especially with:
» hypothermia and drowning,
» poisoning or medicine overdose,
» neurotoxic envenomation (e.g. black and green mamba or Cape cobra snakebite) – see PHC STG Section 21.3.1.4: Snakebites.

This decision should take into consideration the potential risk that CPR poses to the rescuer e.g. infectious diseases.

20.2 POST CARDIAC ARREST CARE

I46.0

DESCRIPTION

Post cardiac arrest care starts following successful CPR. During this time the patient is vulnerable to several processes, including:

» the underlying disease condition or injury causing the cardiac arrest
» post cardiac arrest haemodynamic instability
» post cardiac arrest brain injury
» the sequelae of global ischaemia and reperfusion.

Care should be aimed at reversing or minimising the above processes to optimise the likelihood of neurologically intact survival.

GENERAL MEASURES

The priorities of management post cardiac arrest include:

Determining the cause of cardiac arrest

» careful history and physical examination,
» bedside tests such as 12-lead ECG, blood glucose, Hb, pulse oximetry, blood gases,
» special investigations such as chest x-ray, eFAST, CT of the brain.

Treating reversible conditions

This will be specific to the presentation and clinical findings.

Evidence of ST elevation myocardial infarction (STEMI) on ECG should prompt urgent treatment. See Section 3.2.1: ST elevation myocardial infarction (STEMI).

Note: Prolonged CPR may be a contraindication to administration of thrombolytic or fibrinolytic agents. Consult a specialist to determine whether referral for percutaneous intervention is possible.

Supportive care and prevention of complications

Airway

» Ensure that the airway is patent and protected.
» Endotracheal intubation may be required in patients that do not rapidly regain consciousness following return of spontaneous circulation.

Breathing

» Maintain oxygen saturation ≥ 94%.
» Avoid hyperoxia by weaning the inspired oxygen concentration to the lowest percentage required to maintain a SpO2 ≥ 94%.
» Maintain PaCO2 within normal range in ventilated patients where feasible.

Circulation

» Correct hypovolaemia if present, with judicious IV fluids.
» Monitor response to fluids: pulse rate, BP, urine output, skin perfusion, development of basal crepitations.

» If hypotension persists despite fluid resuscitation, in the absence of ongoing blood loss, commence inotropes (e.g. adrenaline (epinephrine)).
» Aim to maintain mean arterial blood pressure (MAP) above 65 mmHg.
» If brain or spinal cord injury is suspected, it is reasonable to increase the target MAP to 80 mmHg.

Neurological care
» Position head up 30 degrees.
» Monitor for seizures. Treat promptly and load with an anti-epileptic agent if seizures occur.

Blood glucose control
» Maintain blood glucose between 8 and 10 mmol/L and avoid hypoglycaemic episodes.

LoE:IIIb[viii]

Temperature control
» Aim for normothermia by preventing fever in unconscious patients in the first 24 hours, using physical cooling methods e.g.: ice packs and fans, and antipyretics.

LoE:IIIb[ix]

Deep vein prophylaxis
» Consider prophylaxis for venous thrombo-embolism, as required. See Section 2.8: Venous thrombo-embolism.

LoE:IIa[x]

MEDICAL TREATMENT

Hypoglycaemia

LoE:IIIb[xi]

- Dextrose 50%, rapid IV injection 50 mL.

Assess clinical status and finger prick glucose level over the next 5–10 minutes.

Hypovalaemia

- Sodium chloride 0.9%.
  - Consider giving a bolus of 1 litre during CPR if an increase in preload may benefit the patient, e.g., hypovolaemic shock, distributive shock, haemorrhagic shock.
  - Cautious fluid administration is advised during CPR if an increase in the preload could be detrimental, e.g., massive pulmonary embolism or cardiac tamponade.

LoE: IIIb[xii]

Hypotension (after volume correction)

- Adrenaline (epinephrine), IV infusion, start at 0.1 mcg/kg/minute titrated according to the response.
  - Dilute 10 mg i.e. 10 ampoules of adrenaline 1:1 000 in 1 L sodium chloride 0.9%.
  - Infuse according to weight and clinical response.
  - Infusion rate: mL/hour:

mcg/kg/minute	Weight in kg						
	50	60	70	80	90	100	110
0.1	30	36	42	48	54	60	66
0.2	60	72	84	96	108	120	132
0.3	90	108	126	144	162	180	198
0.4	120	144	168	192	216	240	264
0.5	150	180	210	240	270	300	330
0.6	180	216	252	288	324	360	396
0.7	210	252	294	336	378	420	462
0.8	240	288	336	384	432	480	528
0.9	270	324	378	432	486	540	594
1	300	360	420	480	540	600	660

LoE:IIIb[xiii]

Seizures

Treat seizures in post cardiac arrest, similar to management of status epilepticus. See Section 14.5: Status epilepticus.

LoE:IIIb[xiv]

Fever

- Paracetamol, oral, 500 mg to 1 g, 4 to 6 hourly as required (to a maximum of 4 g in 24 hours).
  - Maximum dose: 15 mg/kg/dose.

LoE:IIIa[xv]

REFERRAL

» Following successful resuscitation, cases should be discussed with a hospital with intensive care facilities for transfer.

» If evidence of myocardial infarction is present or if strongly suspected, cases should be discussed with a cardiology service.

20.3 CARDIAC DYSRHYTHMIAS

See Section 3.3: Cardiac dysrhythmias.

MEDICAL EMERGENCIES

Emergency health conditions are those requiring rapid intervention to avert death or disability, and for which treatment delays of hours or less make interventions less effective. Concern that such a condition exists requires urgent assessment.

20.4 ACUTE CORONARY SYNDROMES

See Section 3.2.1: ST elevation myocardial infarction (STEMI) and 3.2.2: Non-ST elevation myocardial infarction (NSTEMI) and Unstable angina (UA).

20.5 ASTHMA, ACUTE

See Section 16.1: Asthma, acute for the management of status asthmaticus.

20.6 ANGIOEDEMA

T78.3 + Y57.9

Contact the 24/7 South African Angioedema Hotline at: 082 091 5684 if you require assistance with acute management, investigation or follow up.

DESCRIPTION

Two major groups of angioedema should be differentiated: allergic angioedema forming part of a systemic reaction to an allergen, and non-allergic angioedema caused by bradykinin excess.

In allergic angioedema, features of allergy or anaphylaxis will often be present, including urticaria, bronchospasm, hypotension or gastrointestinal upset. Anaphylaxis should be treated urgently. See Section 20.7: Anaphylaxis/anaphylactic shock.

Non-allergic angioedema is most commonly caused by ACE-inhibitors in susceptible individuals. It may also be caused by hereditary angioedema or acquired C1 esterase deficiency. Associated features of allergy are absent.

Symptoms

Swelling usually occurs around eyes and lips but may occur elsewhere.

Life-threatening airway obstruction can occur with angioedema of upper airways.

GENERAL MEASURES

Stop all suspected agents, e.g. ACE-inhibitor.

In case of angioedema with airway obstruction, early airway management is essential. If oedema is extensive or progressive, establish a definitive airway. The most skilled person available must handle airway interventions.

Avoid re-exposure to the offending agent and provide an alert bracelet.

MEDICINE TREATMENT

In severe cases of hypersensitivity where airway obstruction may be imminent:

Note: A definitive airway may be required before patient responds to medical treatment. Low threshold to surgical airway tracheostomy.

In cases where angioedema is part of anaphylaxis, treat as anaphylaxis. See Section 20.7: Anaphylaxis/Anaphylactic shock.

If urticaria and/or itch present (no imminent airway compromise):

- Promethazine, IM/IV, 25–50 mg as a single dose. *LoE:IIIb*[xvi]

ADD

- Hydrocortisone, IV, 100 mg as a single dose. *LoE:IIIb*[xvii]

Severe ACE-inhibitor induced angioedema with threatened airway:
Note: A definitive airway may be required before patient responds to medical treatment. Low threshold to surgical airway tracheostomy.

- Lyophilised plasma, IV, 2 units. *LoE:IVb*

If lyophilised plasma is unavailable:

- FFP, IV, 2 units. *LoE:IIIa*[xviii]

Observe all cases until resolution.

20.7 ANAPHYLAXIS/ANAPHYLACTIC SHOCK

T78.2 + Y57.9

DESCRIPTION

An acute, potentially life-threatening hypersensitivity reaction.
The reaction usually starts within seconds to minutes after administration of, or exposure to a substance to which the individual has been sensitised.
Clinical manifestations range from mild urticaria and angioedema to upper airway obstruction, bronchospasm, hypotension, shock and death.
The reaction can be short-lived, protracted or biphasic, i.e. acute with recurrence several hours later.
Immediate reactions are usually the most severe and/or life threatening.

GENERAL MEASURES

Remove the inciting cause (e.g., stop infusion of medicine that caused anaphylaxis).
Administer adrenaline (epinephrine) immediately (see below)
Cardiopulmonary resuscitation, if required.
Maintain an open airway. Intubate, if necessary.
Monitor all vital parameters (including pulse and blood pressure) closely.
Reassure and comfort the patient.
Counsel patient to prevent recurrence.
Patient should wear an alert bracelet at all times.

Anaphylaxis associated with vaccinations:

» Always keep a fully equipped emergency tray at the vaccination point.
» It is advisable to observe clients for 15 minutes after a vaccination. If a client is known with severe allergies, an observation period of 30 minutes is advised.
» Clients who develop symptoms should be assessed for possible vaccination associated anaphylaxis by considering the following:
  - If signs and symptoms are generalised – involving more than 2 body systems, manage as anaphylaxis.

- If signs and symptoms are serious or life-threatening (including hypotension, respiratory distress significant swelling of lips or tongue), even if only one body system is involved, treat as anaphylaxis.
- If isolated rash in an otherwise well client, monitor for 30 minutes.

» Clients who collapse following vaccination:
- Call for help and put patient on his/her back and raise legs.
- Check if responsive – if unresponsive, commence CPR (See Section 20.1: Cardiac arrest in adults)
- A vasovagal episode is usually associated with a transient loss of consciousness (< 1 minute), relieved by raising the legs when supine, transient low BP and low HR.
- Collapsing after vaccination usually occurs 5-10 minutes post-vaccination, but can occur up to an hour afterwards.
- Treat as anaphylaxis if loss of consciousness is not brief and not relieved by raising the legs, or when any of the warning signs for anaphylaxis occur.

		ACUTE STRESS RESPONSE	
	ANAPHYLAXIS	GENERAL	VASOVAGAL REACTION WITH SYNCOPE
Onset	Usually 5 min after immunization but may be delayed up to 60 min	Sudden, occurs before, during or shortly after (< 5 min) immunization	Sudden, occurs before, during or shortly after (< 5 min) immunization. May present after 5 min if the individual stands suddenly.
System			
Skin	Generalized urticaria (hives) or generalized erythema, angioedema, localized or generalized, generalized pruritus with or without skin rash, generalized prickle sensation, localized injection site urticaria, red and itchy eyes	Pale, sweaty, cold, clammy	Pale, sweaty, cold, clammy
Respiratory	Persistent cough, noisy breathing and airway constriction: wheeze, stridor. If very severe, respiratory arrest.	Hyperventilation (rapid, deep breathing)	Normal to deep breaths
Cardiovascular	↑ heart rate, ↓ blood pressure, circulatory arrest	↑heart rate, normal or ↑systolic blood pressure	↓ heart rate with or without transient ↓in blood pressure
Gastrointestinal	Nausea, vomiting, abdominal cramps	Nausea	Nausea, vomiting
Neurological and other symptoms	Uneasiness, restlessness, agitation, loss of consciousness, little response when supine or lying flat	Fearfulness, light-headedness dizziness, numbness, weakness, tingling around the lips, spasms in hands, feet	Transient loss of consciousness, good response once supine or lying flat, with or without tonic–clonic seizure

Table 20.1.: Differences between anaphylaxis, general acute stress response and vasovagal reaction with syncope

Source: Immunization stress-related response. A manual for program managers and health professionals to prevent, identify and respond to stress related responses following immunization. Geneva: World Health Organization; 2019. https://apps.who.int/iris/handle/10665/330277

MEDICINE TREATMENT

- Adrenaline (epinephrine) 1:1 000, 0.5 mL, IM, immediately into anterolateral thigh.
  - Repeat dose every 5 minutes, as required.

In cases of persistent hypotension or where multiple repeat doses are required:

- Adrenaline (epinephrine), IV infusion, start at 0.05 mcg/kg/minute titrated according to the response.
  - Dilute 10 mg i.e. 10 ampoules of adrenaline 1:1 000 in 1 L sodium chloride 0.9%.
  - Infuse according to weight and clinical response.
  - Infusion rate: mL/hour:

mcg/kg/minute	Weight in kg						
	50	60	70	80	90	100	110
0.05	15	18	21	24	27	30	33
0.1	30	36	42	48	54	60	66
0.2	60	72	84	96	108	120	132
0.3	90	108	126	144	162	180	198
0.4	120	144	168	192	216	240	264
0.5	150	180	210	240	270	300	330
0.6	180	216	252	288	324	360	396
0.7	210	252	294	336	378	420	462
0.8	240	288	336	384	432	480	528
0.9	270	324	378	432	486	540	594
1	300	360	420	480	540	600	660

LoE:IVb

AND

- Hydrocortisone, IV/IM, 200 mg, immediately as a single dose.

AND

Intravenous fluids

LoE:IIa[xix]

Establish an intravenous line:

- Sodium chloride 0.9%, IV.

If bronchospasm:

- Oxygen if saturation <94%. *LoE:IIb*[xx]

AND

- Salbutamol, nebulisation, 5 mg.
  - Nebulise continuously (refill the nebuliser reservoir every 20 minutes) at a flow rate of 6–8 L/minute. *LoE: IVb*[xxi]

AND

- Ipratropium bromide, nebulisation 0.5 mg, added to salbutamol solution.

LoE: IVb[xxii]

If urticaria and/or itch present:

- Antihistamine, e.g.:
- Promethazine, IV 25–50 mg as a single dose.

LoE:IIIb[xxiii]

OR

- Cetirizine, oral, 10 mg as a single dose.

20.8 DELIRIUM

F05.0-1/F05.8-9/R45.1/R45.4-6

DESCRIPTION

Delirium is a disturbance in attention, awareness (reduced orientation to the environment), and cognition (e.g. memory deficit, language, visuospatial ability, or perception). It is acute, developing within hours to days, and fluctuates during the day, worsening in the evenings. It may be hyperactive, with increased mood lability, agitation, and/or uncooperative behavior, or hypoactive, with poor responsiveness and stupor.

Delirium should not be mistaken for a psychiatric disorder. It is a physiological consequence of another medical condition, substance intoxication or withdrawal (including prescription or over the counter medications and recreational substances), exposure to a toxin, or multiple etiologies. Risk factors include:

» > 65 years of age,
» dementia,
» history of previous delirium or of falls,
» history of stroke, epilepsy, or other neurological disorders,
» HIV infection,
» multiple comorbidities,
» medicines such as anticholinergics, hypnotics, and opioids,
» polypharmacy,
» psychoactive substance use,
» severe illness.

GENERAL MEASURES

» Investigations need to be done to exclude or diagnose an underlying medical problem, **the treatment of which is the primary management.**

Checklist for diagnosis:

D Drugs (Intoxication and withdrawal. Consider Wernicke's encephalopathy).
I Infections, e.g. sepsis, pneumonia, urinary tract infections, peritonitis, meningitis.
M Metabolic, e.g. hypoglycaemia, electrolyte abnormalities (e.g. hyponatraemia); organ failure (e.g. liver failure, renal dysfunction), CO_2 narcosis.
T Trauma, e.g. chronic subdural haematoma.
O Oxygen deficit (including hypoxia, carbon monoxide poisoning).
P Psychiatric or physical conditions, e.g. severe stressor pain.

» Assess for and address dehydration, constipation, hypoxia, infections, pain, and discomfort.

» Avoid abrupt substance withdrawal (see Adult Hospital STGs and EML; Chapter 15: Mental Health conditions, Substance misuse).
» Review all medicines that the person has been taking – optimise doses; gradually wean and stop any unnecessary medication, including sedatives and analgesics.

Nursing interventions:
» Nurse in calm, predictable environment, avoid changes of staff or rooms.
» Maintain circadian rhythm: in the day mobilise, provide sensory stimulation/ spectacles/ hearing aids; at night avoid noise, light and procedures.
» Ensure effective communication: introduce self with each patient contact, be aware of patient's non-verbal cues, listen attentively, reassure frequently.
» Re-orientate verbally, with a clock, and signage.

CAUTION – Physical restraint
» Worsens the outcomes of delirious patients: this is a last resort when all else has failed and is a short-term measure until chemical restraint and other measures have been achieved.
» Manual restraint: respectful, controlled, applied by personnel of the same sex as the patient.
» Mechanical restraint: only if absolutely necessary to protect the patient and others for as short a time as possible. Document the type, sites and duration of any restraints used. 15-minute monitoring of vital signs, the mental state, restraint sites, and reasons for use.

MEDICINE TREATMENT
» Treat the underlying medical or surgical condition.
» Keep antipsychotic or benzodiazepine use to a minimum.
» Use small doses regularly rather than large doses less frequently.
» Adjust doses according to clinical circumstances, e.g., lower doses in the elderly, debilitated, or where HIV infection or HIV-related dementia is known or suspected.

Acute management
For management of severe aggression and disruptive behaviour: see Section 15.1: Aggressive disruptive behaviour in adults.

For agitated and acutely disturbed patient:
- Haloperidol, oral, 0.75–1.5 mg twice daily.
  - May be repeated 4 hourly if needed to a maximum dose of 10mg in 24 hours.
  - May be continued short-term (usually 7 days or less) at lowest dose at which behaviour is contained.

OR
If unable to swallow or oral medication declined:
- Haloperidol, IM, 0.5–1mg.

- May be repeated after 30–60 minutes if needed and then 4 hourly, to a maximum dose of 10mg in 24 hours.
- Monitor vital signs and beware of acute dystonia, other extra-pyramidal side effects, and neuroleptic malignant syndrome.

OR

If haloperidol, IM is not available: *LoE:IVb[xxiv]*

- Olanzapine, oral dispersible tablet or IM, 2.5–5 mg.
  - This can be repeated in 30–60 minutes, if required and then 6 hourly, to a maximum dose of 20 mg within 24 hours.
  - Monitor vital signs and beware of oversedation, neuroleptic malignant syndrome, and acute dystonia.

OR

For substance withdrawal, Parkinson's disease, or intolerability to haloperidol or olanzapine:

- Benzodiazepine, repeat as necessary, to achieve containment, e.g.:
- Lorazepam, IM, 0.25–1 mg, 2 to 4 hourly, maximum dose 3 mg in 24 hours

OR

- Clonazepam, IM, 0.5–2 mg.

OR

- Diazepam, IV, 5–10 mg. *LoE:IIIb[xxv]*
  - Switch to oral route once containment is achieved.
  - In the elderly, a starting dose of 2 mg is recommended

CAUTION - Benzodiazepines

» Can cause respiratory depression, especially diazepam IV.
» Can aggravate delirium.
» In the frail and elderly patient or where respiratory depression is a concern, reduce the dose by half. *LoE:IVb[xxvi]*
» The safest route of administration is oral followed by IM; IV route has the highest risk of respiratory depression and arrest.
» Monitor vital signs closely during and after administration.
» Allow at least 15–30 minutes for the medication to take effect. Repeated IM doses of benzodiazepines may result in toxicity owing to accumulation.

If alcohol withdrawal/ Wernicke's encephalopathy suspected:

- Thiamine, IM, 200 mg immediately. *LoE:IVb[xxvii]*

20.9 DIABETIC EMERGENCIES

See Sections 8.6.1: Hypoglycaemia and 8.6.2: Diabetic ketoacidosis (DKA) and hyperosmolar hyperglycaemic state (HHS).

20.10 PULMONARY OEDEMA, ACUTE

J81

DESCRIPTION

A life-threatening condition with abnormal accumulation of fluid in the lungs.
Common causes include acute decompensation of chronic underlying heart failure and acute renal failure (e.g. acute nephritis).
Patients with acute decompensated heart failure appear extremely ill, restless, poorly perfused and sweaty, tachypnoeic, tachycardic, and hypoxic, with increased work of breathing, and frothy sputum.

GENERAL MEASURES

Maintain open airway. Consider non-invasive positive pressure ventilation.
Position in Fowler's position, unless hypotensive or comatose.
Correct electrolyte disturbances.
Determine and correct any dysrhythmias.

MEDICINE TREATMENT

- Administer oxygen using face mask to deliver 40% oxygen at a rate of 6–8 L per minute.

Fluid overload suspected/detected:

- Furosemide, slow IV, 40 mg.
  - If response is adequate, follow with 40 mg in 2–4 hours.
  - If no response within 20–30 minutes: furosemide, IV, 80 mg.

Followed by:

- Nitrates, e.g.: *LoE:IVb*
- Isosorbide dinitrate, SL, 5 mg repeat every 5–10 minutes, if necessary.
  - Monitor blood pressure. Do not administer if hypotensive.

OR

- Glyceryl trinitrate, IV, 5–200 mcg/minute, titrated to response.
  - Guidance on preparation and administration included below.

CAUTION
Glyceryl trinitrate IV formulation must be diluted before infusion

STEP 1: Select the concentration as required for the individual patient
- For patients who are fluid congested or require higher doses for a clinical response, consider using a more concentrated solution e.g. 200 or 400 mcg/mL.

STEP 2: Select the volume of the diluent
- Patients who are likely to require treatment for a longer duration e.g. unstable angina prepare a larger volume e.g. 500mL.
- Compatible diluents include sodium chloride 0.9% or dextrose 5%.

STEP 3: Confirm the formulation of glyceryl trinitrate available and mix with diluent
- Confirm the strength of the GTN solution i.e. whether a 1mg/mL or 5mg/mL formulation is available.

- Depending on the formulation available, select the number of ampoules to be used based on the concentration and volume of the diluent as decided in Step 1 and 2 above.
- Ensure that the equivalent volume of diluent is removed from the bag before adding the total GTN volume e.g. if 100mLs of GTN is to be added, first remove 100mL of diluent from the bag before adding the GTN.

STEP 4: Set the flow rate for infusion

- Flush the PVC tube before administering to patient.
- Start with the lowest flow rate possible based on the concentration of the solution prepared.
- Increase by 5 mcg/minute every 5 minutes until response achieved or until the rate is 20 mcg/minute.
- If no response after 20 mcg/minute increase by 20 mcg/minute until response. Monitor blood pressure carefully.

E.g. To prepare a 200mcg/mL solution for a patient likely to require several hours of the GTN infusion:

Use 10 ampoules (100mL) of the 1mg/mL GTN formulation mixed with 400mL of diluent (100mL to be removed from a 500mL bag). Initiate the infusion at a flow rate 3mL/hr and titrate the infusion rate based on the patient's response.

STEP 1	**STEP 2**	**STEP 3**			
Concentration of dilution	**Volume of diluent**	**Glyceryl trinitrate 1 mg/mL**		**Glyceryl trinitrate 5 mg/mL**	
		Volume (Dose)	Number of 10mL ampoules	Volume (Dose)	Number of 10mL ampoules
100 mcg/mL	250 mL	25 mL (25 mg)	2.5	5 mL (25 mg)	0.5
200 mcg/mL		50 mL (50 mg)	5	10 mL (50 mg)	1
400 mcg/mL		100 mL (100 mg)	10	20 mL (100 mg)	2
100 mcg/mL	500 mL	50 mL (50 mg)	5	10 mL (50 mg)	1
200 mcg/mL		100 mL (100 mg)	10	20 mL (100 mg)	2
400 mcg/mL		200 mL (200 mg)	20	40 mL (200 mg)	4

STEP 4	**Solution concentration (mcg/mL)**	**100 mcg/mL solution**	**200 mcg/mL solution**	**400 mcg/mL solution**
	Dose (mcg/min)	Flow rate (microdrops/min = mL/hr)		
	5	3	–	–
	10	6	3	–
	15	9	–	–
	20	12	6	3
	30	18	9	–
	40	24	12	6
	60	36	18	9

	80	48	24	12
	100	60	30	15
	120	72	36	18
	160	96	48	24
	200	–	60	30

No fluid overload present:
Initiate nitrates, followed by furosemide.

If hypotensive consider inotropic support, e.g.:

- Dobutamine, IV infusion, 5–20 mcg/kg/minute.
  - Dilute 1 vial (250 mg/20 mL) up to 50 mL with sodium chloride 0.9% or dextrose 5%. (Solution = 5 mg/mL or 5 000 mcg/mL)
  - Administer under constant ECG monitoring.
  - Rate of infusion in mL/hour: see weight-dose table in Section 20.12.3: Cardiogenic shock.
  - Monitor the blood pressure continuously.

CAUTION
Do not use morphine for pulmonary oedema, as there is observational data providing a signal of harm.

LoE:IIIb[xxviii]

20.11 RAPID SEQUENCE INDUCTION AND INTUBATION

Anaesthetic and sedative medication may be administered only by medical practitioners trained and experienced in their use. Sound theoretical and practical training followed by supervised experience in the administration of anaesthetic and sedative medication is essential. Even within the recommended dosage range, anaesthetic agents can cause death when inappropriately used. *LoE:IVb*[xxix]

Medicines and equipment for resuscitation should be functional and immediately available whenever general anaesthesia, regional anaesthesia, or sedation is administered.

The doses of the medicines given are those recommended for healthy adults. Patients who are acutely or chronically sick, and/or elderly, may require substantial reductions in the doses given otherwise life-threatening adverse effects may ensue.

Patients at risk of aspiration require a rapid sequence intubation. An IV induction agent is given through an IV line with fast running fluids, immediately followed by a rapidly acting muscle relaxant. The rapid onset of action enables the time to intubation to be short enough to avoid mask ventilation, as this can result in gastric insufflation and aspiration of gastric contents.

20.11.1 INDUCTION AGENTS

Z99.1

Respiratory depression occurs following induction of anaesthesia and ventilation should be supported as required.

Administer at appropriate doses, after consideration of patient factors and contraindications:

» Propofol is the most widely used IV induction agent but can produce hypotension.

» Etomidate or ketamine is preferred in haemodynamically unstable patients.

LoE:IVb[xxx]

- Propofol, IV, 1.5–2.5 mg/kg.
- Etomidate, IV, 0.3 mg/kg (0.2–0.6 mg/kg)
- Ketamine, IV, 1–2 mg/kg.

20.11.2 MUSCLE RELAXANTS

Z99.1

- Suxamethonium, 1–1.5 mg/kg, IV. (See Section 12.3.1: Depolarising muscle relaxants.)
  - Preferred agent as, in the event of a failed intubation, it wears off quickly enabling spontaneous respiration to resume.
  - Contraindications to suxamethonium
    - Congenital and acquired medical conditions associated with severe, potentially lethal suxamethonium-induced hyperkalaemia.
    - Malignant hyperthermia.

LoE:IIb[xxxi]

<u>If suxamethonium is contra-indicated, consider:</u>

- Rocuronium, 0.9 mg/kg, IV.
  - Duration +/- 60 minutes.

LoE:IIb[xxxii]

Prolonged effect can be problematic in the event of a difficult or failed intubation and if the procedure is short.

20.11.3 POST-INTUBATION SEDATION

Z99.1

Sedation requirements fluctuate rapidly and warrant regular review. Individualised sedation objectives should be clearly defined, and level of sedation regularly recorded. Sedation protocols that recognise the need for dose minimisation, weaning, and sedation interruptions probably improve outcomes.

LoE:IIIb[xxxiii]

Adequate pain control is often more efficacious than sedatives for reducing agitation. The doses listed apply to ventilated patients in whom short term respiratory depression is not a concern.

Sedation

<u>Short term sedation (less than 24 hours)</u>

- Midazolam, IV infusion, 0.05–0.2 mg/kg/hour.

OR

- Propofol, IV infusion, 0.5 mg/kg/hour. LoE:IVb[xxxiv]

Note: Propofol has cardiovascular effects; benzodiazepines are preferred. LoE:IIIb[xxxv]

Longer term sedation (expected 72 hours or more)

- Midazolam, IV, 0.2 mg/kg/hour.

OR

- Lorazepam, IV, 0.1 mg/kg/hour.

Note: Lorazepam (0.1 mg/kg/hour) is as effective (and as easy to wean) as midazolam 0.2 mg/kg/hour) but is more difficult to titrate. Due to high fat solubility, midazolam also becomes 'long acting' after infusions of more than 24 hours.

Supplemental analgesia:

ADD an analgesic to any of the above regimens:

- Morphine, IV infusion, 0.1–0.2 mg/kg/hour.

OR

- Fentanyl, IV infusion, 1 mcg/kg/hour (also becomes long acting after prolonged infusion due to fat solubility).

OR

- Ketamine, IV infusion, 0.5–1 mg/kg/hour.

Note: If haemodynamically unstable, use adjunctive ketamine for analgosedation. LoE:IIIb[xxxvi]

20.12 SHOCK

20.12.1 HYPOVOLAEMIC SHOCK

20.12.1.1 NON-TRAUMA RELATED HYPOVOLAEMIC SHOCK

R57.1

DESCRIPTION

This happens when there is loss of intravascular fluid, e.g. severe diarrhoea and dehydration, haemorrhage, or fluid shifts.

GENERAL MEASURES

Control obvious bleeding with direct pressure.
Insert one or two large bore IV catheters; peripheral lines are adequate.

MEDICINE TREATMENT

NON-TRAUMA RELATED LoE:IIa[xxxvii]

- Sodium chloride 0.9%, IV, 1–2 L.
  - Monitor blood pressure, pulse and clinical response.

20.12.1.2 TRAUMA-RELATED HYPOVOLAEMIC SHOCK

T79.4 + R57.1

DESCRIPTION

Shock is inadequate perfusion of the vital organs. Clinically this may manifest with hypotension, tachycardia, weak pulses, clammy skin, pallor, altered mental state, poor urine output and elevated lactate.

The presence of shock in a patient with bleeding indicates that a significant volume of blood has already been lost.

The common traumatic sites of blood loss include the chest, abdomen, pelvis, long bone fractures, and vascular injuries.

Major non-traumatic bleeds include gastrointestinal haemorrhage, ruptured ectopic pregnancy and obstetric haemorrhage.

GENERAL MEASURES

Control bleeding. Techniques may include:

» Direct, sustained pressure over the bleeding point.
» Use of tourniquets in exsanguinating limb haemorrhage, e.g. manual BP cuff or specialized tourniquet while awaiting transfer to theatre. (Do not use for longer than 6 hours).
» Tamponade techniques e.g. inflated Foley catheter in neck, axilla or femoral wounds.

Obtain large bore IV access, preferably two lines.

Prevent hypothermia.

Send blood sample to blood bank as early as possible for blood type and screening. Notify blood bank of possible massive transfusion.

MEDICINE TREATMENT

- Oxygen if saturation <94%. *LoE:IIb*[xxxviii]

Trauma related

- Sodium chloride 0.9%, IV. *LoE:IIa*[xxxix]

<u>If more than 1 litre of fluid is needed, consider blood products:</u>

» In cases of major bleeding, limit fluid volumes to less than 1.5 litres in total where possible. Replace acute blood loss with blood and blood products.
» Emergency blood should be used in unstable patients and when there will be significant delay in obtaining cross-matched blood from a blood bank.
» Rh typing is advised when possible.
  – Type O Rh negative blood should be reserved for women of child-bearing age that are Rh negative or Rh status unknown.
  – Type O Rh positive blood may be given to Rh positive women of child-bearing age, females >50 years of age or males regardless of Rh status.
» After 2 units of emergency blood, consider activation of massive transfusion protocol. See Section 20.12.1.2.1: Massive transfusion.

20.12.1.2.1 MASSIVE TRANSFUSION

Z51.8

DESCRIPTION

A massive transfusion is the replacement of a patient's blood volume or 10 units over a 24-hour period, or replacement of half of that volume over 4 hours.

GENERAL MEASURES

Actively treat and prevent hypothermia.

When it is anticipated that large volumes of blood will be required, the replacement of platelets and clotting factors in addition to red blood cells is needed to prevent coagulopathy.

MEDICINE TREATMENT

Facilities without access to a blood bank:

- Lyophilised plasma, IV.
  - 1 unit for each unit of emergency blood transfused.

Arrange urgent transfer to a centre with blood bank and specialist services.

Facilities with access to a blood bank:

» Ensure that the blood bank receives an appropriate specimen as soon as the possible need for transfusion is identified.

» Notify the blood bank as soon as possible of the need for a massive transfusion and request a massive transfusion pack.

A massive transfusion pack will typically consist of:

- Red blood cells (RBCs), 6 units. *LoE:IVb*

AND

- Lyophilised plasma, IV.
  - 1 unit for each unit of emergency blood transfused.

OR

- FFP, 6 units - thawed when requested.

AND

- Platelets, 1 mega-unit (normally 6 pooled donor units).
  - Aim to transfuse the above products in a 1:1:1 ratio, or as guided by laboratory parameters.
  - Send specimens for FBC and INR and continue to monitor.

LoE:IVb[xi]

Expedite definitive control of bleeding:

- Tranexamic acid, IV, 1 g, infused over 10 minutes.
  - Followed with IV infusion, 1 g, over 8 hours. *LoE:Ia*[xii]
  - Benefit is greatest if initiated in the 1st hour. Initiation of tranexamic acid more than 3 hours after the initial trauma may be harmful.

If patient responds initially and subsequently deteriorates, there may be an ongoing occult haemorrhage. If no response occurs, consider:

» Occult exsanguinating haemorrhage: intra-abdominal, retroperitoneal and intrapleural.

» Non-hypovolaemic shock: tension pneumothorax, myocardial contusion, cardiac tamponade, or myocardial infarct.

20.12.2 DISTRIBUTIVE SHOCK

This happens when the blood vessels are abnormally dilated and presents with a low blood pressure, tachycardia and warm peripheries. There are 3 causes of this type of shock:
» neurogenic shock,
» septic shock, and
» anaphylactic shock (see Section : 20.7 Anaphylaxis/anaphylactic shock).

20.12.2.1 NEUROGENIC SHOCK

T09.3 + R57.8

DESCRIPTION

Occurs in spinal cord trauma when there is an interruption of the sympathetic chain causing vasodilatation.

GENERAL MEASURES

Check circulation, airway and breathing.
Spinal cord immobilisation.
Exclude other injuries that could cause low blood pressure.

MEDICINE TREATMENT

- Oxygen if saturation <94%. *LoE:IIb*[xlii]
- Sodium chloride 0.9%, IV. *LoE:IIa*[xliii]
  - Administer crystalloid in titrated boluses up to 1 litre.
- Adrenaline (epinephrine), IV infusion, start at 0.05 mcg/kg/minute titrated according to the response. *LoE:IVb*
  - Dilute 10 mg (10 ampoules) of adrenaline 1:1 000 in 1 L sodium chloride 0.9%.
  - Infuse according to weight and clinical response.
  - Infusion rate: mL/hour:

mcg/kg/minute	Weight in kg						
	50	60	70	80	90	100	110
0.05	15	18	21	24	27	30	33
0.1	30	36	42	48	54	60	66
0.2	60	72	84	96	108	120	132
0.3	90	108	126	144	162	180	198
0.4	120	144	168	192	216	240	264
0.5	150	180	210	240	270	300	330
0.6	180	216	252	288	324	360	396
0.7	210	252	294	336	378	420	462
0.8	240	288	336	384	432	480	528
0.9	270	324	378	432	486	540	594

1	300	360	420	480	540	600	660

20.12.2.2 SEPTIC SHOCK

R57.2

DESCRIPTION

Shock caused by a confirmed or suspected infection, with vasodilatation, increased capillary permeability, and decreased contractility of the heart.

GENERAL MEASURES

Check airway, breathing and circulation.

MEDICINE TREATMENT

- Oxygen if saturation <94%. *LoE:IIb*[xliv]

Take blood culture (or any other tissue/body fluid), then administer appropriate parenteral broad-spectrum antibiotics urgently, e.g.:

- Ceftriaxone, (W) IV, 2 g daily. *LoE:IIIb*[xlv]

Perform a fluid challenge for hypotension:

- Sodium chloride 0.9%, 500 mL boluses over 30 minutes, whilst monitoring clinical response until 30 mL/kg has been administered.
  - Assess BP and pulse rate response. Response is defined by a good urine output (>0.5 mL/kg/hour) and adequate cerebral perfusion rather than an absolute BP value.

Balanced solutions may be appropriate in some patients (i.e. presentation with hyponatraemia, previous renal placement therapy): *LoE:Ia*[xlvi]

- Balanced solution, e.g.:
- Ringer's lactate, 500 mL boluses over 30 minutes, whilst monitoring clinical response, until 30 mL/kg has been administered.
  - Assess blood pressure and pulse rate response. Response is defined by a good urine output (>0.5 mL/kg/hour) and adequate cerebral perfusion rather than an absolute blood pressure value.

Avoid over-hydrating as this could exacerbate hypoxia associated with adult respiratory distress syndrome.

If no haemodynamic response to early aggressive fluid resuscitation:

- Adrenaline (epinephrine), IV infusion, 0.05 mcg/kg/minute titrated according to the response.
  - Dilute 10 mg (10 ampoules) of adrenaline 1:1000 in 1 L sodium chloride 0.9%.
  - Infuse according to weight and clinical response. (Aim for target MAP 65 mmHg and urine output 0.5 mL/kg/hour.)
  - See Section 20.12.2.1: Neurogenic shock, for the infusion rate.

20.12.3 CARDIOGENIC SHOCK

R57.0

DESCRIPTION

Patients are hypotensive, cold and clammy and their pulse rate may be variable. Causes include an acute myocardial infarction, myocardial contusion, myocarditis, dysrhythmias, valvular heart disease, aortic dissecting aneurysm etc.
Consult with specialist and consider referring patients after initial emergency measures have been taken.

GENERAL MEASURES

Check circulation, airway and breathing.
ECG.
Treat the underlying cause, e.g.: MI, dysrhythmia, etc.

MEDICINE TREATMENT

- Oxygen if saturation <94%. *LoE:IIb*[xlvii]

A right ventricular myocardial infarction may respond to a fluid challenge:

- Sodium chloride 0.9%, IV. *LoE:IIa*[xlviii]
  - Administer 250–500 mL as a bolus and assess fluid responsiveness.
- Dobutamine, infusion, 5–10 mcg/kg/minute.
  - Dilute 1 vial (250 mg/20 mL) up to 50 mL with sodium chloride 0.9% or dextrose 5% (5 mg/mL or 5 000 mcg/mL).
  - Monitor the blood pressure.
  - Rate of infusion in mL/hour: *LoE:IVb*[xlix]

	Weight (kg)									
Dose mcg/kg/min	30	40	50	60	70	80	90	100	110	120
2	0.9	1.2	1.5	1.8	2.1	2.4	2.7	3	3.3	3.6
5	1.8	2.4	3	3.6	4.2	4.8	5.4	6	6.6	7.2
7.5	2.7	3.6	4.5	5.4	6.3	7.2	8.1	9	9.9	10.8
10	3.6	4.8	6	7.2	8.4	9.6	10.8	12	13.2	14.4

20.12.4 OBSTRUCTIVE SHOCK

R57.8

DESCRIPTION

Occurs when there is an obstruction to the filling of the right ventricle or an obstruction in blood flow. Clinical signs include hypotension, tachycardia, cold peripheries and distended neck veins.

Causes include:

» cardiac tamponade,
» acute pulmonary embolism, and
» tension pneumothorax,
» severe bronchospasm.

TREATMENT

Treat the cause.
Acute pulmonary embolism and cardiac tamponade require urgent consultation with a specialist and referral after initial emergency measures have been taken

20.13 STATUS EPILEPTICUS

See Section 14.5: Status epilepticus.

TRAUMA AND INJURIES

For trauma-related haemorrhage, presenting within 3 hours of injury, see Section 20.12.1: Hypovolaemic shock.

20.14 ACUTE KIDNEY INJURY

See Section 7.1.4: Acute kidney injury.

20.15 BITES AND STINGS

See Chapter 19: Poisonings – envenomation.

20.16 BURNS

T30.0-3 + T31.0-9

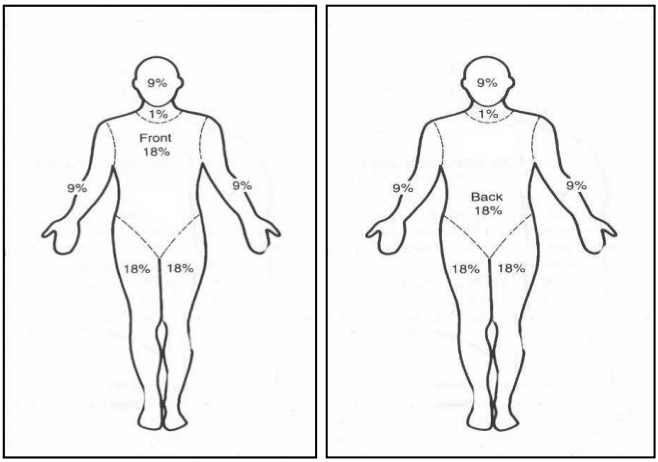
DESCRIPTION

Skin and tissue damage caused by:
» exposure to extremes of temperature,
» contact with an electrical current,
» exposure to a chemical agent, or
» radiation.

ASSESSMENT OF BURNS

Depth of burn wound	SURFACE /COLOUR	PAIN SENSATION/HEALING
Superficial or epidermal	Dry, minor blisters, erythema	» Painful » Heals within 7 days
Partial thickness superficial or superficial dermal	Blisters, moist	» Painful » Heals within 10–14 days
Partial thickness deep or deep dermal	Moist white or yellow slough, red mottled	» Less painful » Heals within a month or more Generally needs surgical debridement and skin graft
Full thickness (complete loss of skin)	Dry, charred whitish, brown or black	» Painless, firm to touch » Healing by contraction of the margins Generally needs surgical debridement and skin graft

The figures below are used to calculate body surface area %.
These diagrams indicate percentages for the whole leg/arm/head/neck not just the front or back.
Children ≥8 years and adults



Source: Karpelowsky JS, Wallis L, Madaree A, Rode H; South African Burn Society. South African Burn Society burn stabilisation protocol. S Afr Med J. 2007 Aug;97(8):574-7. http://www.ncbi.nlm.nih.gov/pubmed/17966146

GENERAL MEASURES

» Assess airway, breathing:
  – Look for signs of inhalational burn- history of hot gas, smoke, steam.
  – INTUBATE if significant airway obstruction present or WORSENING symptoms.
  – Intubation is necessary in the case of unconscious patients, hypoxic patients with severe smoke inhalation, or patients with flame or flash burns involving the face and neck if there is evidence of compromised airway patency.
  – Intubate early if burns are inhalational, or in the presence of pharyngeal burns with soft tissue swelling, as these patients frequently develop respiratory failure.
  – Close monitoring is essential during the first 24-48 hours.
  – If breathing is compromised because of tight circumferential trunk burns, consult with burn centre surgeons immediately. Urgent escharotomies may be required to facilitate chest expansion.
» Assess circulation:
  – Establish large-bore intravenous (IV) lines and provide resuscitation bolus fluid.

  - Reminder: IV lines may be placed through the burned area if necessary (suture to secure).
» Assess neurological state of the patient.
» Assess for associated trauma related injuries
  - Secure the C–spine with an inline stabilising collar, when the mechanism of injury could indicate additional trauma.
  - Identify potential sources of internal bleeding.
  - Stop any external bleeding.
» Remove any sources of heat or chemicals. Removal constrictive clothing/accessories.
» Estimate percentage of total body surface area involved.
» Support vital organ function.
» Look for aggravating comorbidities, e.g. seizures, hyperkalaemia, renal failure.
» Assess need for decompression incisions: escharotomies.
» Local wound care: Clean superficial burns can be managed by occlusive dressings. Deeper wounds may have to be excised and grafted.
» Rehabilitation involving physiotherapy and occupational therapy.

Local wound care
» Melted plastic and tar can be removed with the topical application of liquid paraffin solution.
» Wash burn wounds with soap and water or 1% chlorhexidine.
» Cool burns less than 3 hours old with cold tap water for at least 30 minutes and then dry the patient.
» Keep the wound clean and dress with sterile dressings.
» If infected burn:
  - Povidone-iodine 5%, cream, applied daily.

For chemical burns
» Remove all clothing.
» Brush powdered chemicals off the wound.
» Flush chemical burns for a minimum of 30 minutes using copious volumes of running water.
» Reminder: Never neutralise an acid with a base or vice versa.
» Determine what chemical (and what concentration) caused the injury.
» Ocular burns: T26.4
  - Sodium chloride 0.9% gentle eye washes or irrigations as soon as possible. Follow with an ophthalmology consultation.

For electrical burns
» Differentiate between low-voltage (<1 000 v) and high-voltage (>1 000 v) injuries.
» Attach a cardiac monitor; treat life-threatening dysrhythmias as needed.
» Suspect compartment syndrome, consider escharotomies.

Nutrition
Burn injuries put patients into a hypermetabolic state which requires early and adequate nutritional support. Seek early guidance from local burns centre. See Section 12.13.1: Nutritional support.

MEDICINE TREATMENT

Fluid replacement
Burns ≤10% Total Body Surface Area (TBSA):
- Oral rehydration solution.

Burns >10% of TBSA:
- Sodium chloride 0.9%, IV fluid for resuscitation, replacement and maintenance.

Calculation of fluid replacement
Replacement fluids for burns
First 24 hours:

- Sodium chloride 0.9%, IV. *LoE:IIa*
  - Calculate total fluid requirement in 24 hours:
    Total % burn x weight (kg) x 4 mL.
  - Give half this volume in the 1st 8 hours.
  - Administer remaining fluid volume in next 16 hours.

Note: If urine output is not adequate, increase fluids for the next hour by 50%. Continue at a higher rate until urine output is adequate, then resume normal calculated rate. Aim for urine output 0.5 mL/kg/hr.

Analgesia
Ensure adequate analgesia particularly at change of dressing, i.e.:
- Morphine, IV, to a total maximum dose of 10 mg (see Appendix II, for individual dosing and monitoring for response and toxicity).

AND
- Paracetamol, oral, 500 mg to 1 g, 4 to 6 hourly as required (to a maximum of 4 g in 24 hours).
  - Maximum dose: 15 mg/kg/dose.

Tetanus prophylaxis Z23.5
- Tetanus toxoid vaccine, IM, 0.5 mL immediately, if not previously immunised within the last 5 years.

Stress ulcer prophylaxis
» Feeding patients provides protection against gastric ulcers developing and prophylaxis is not necessary in patients who are tolerating feeds.
» Stress ulceration, a complication of critical illness, needs to be prevented.
» Oral or enteral feeding should be initiated as soon as possible.
- Pantoprazole, 40mg, IV daily.
  - Stop stress ulcer prophylaxis once the patient is tolerating enteral feeds.

Note: Pharmacokinetic parameters are altered in patients with severe burns, notably an increased volume of distribution. An appropriate loading dose should be given of certain medicines, e.g. aminoglycosides. Therapeutic drug monitoring (TDM) may inform dosing and should be requested, if available.

Discuss the following cases with a burns specialist:

» Burns >15% body surface area (BSA) or >10% BSA >50 years of age.
» Burns of face, hands, feet, genitalia, perineum or involving joints.
» Electrical burns, including lightning burns.
» Chemical burns.
» Inhalation injury or burns.
» Burns associated with major trauma.
» Circumferential burns.

20.17 EXPOSURE TO POISONOUS SUBSTANCES

See Chapter 19: Poisoning.

20.18 EYE INJURIES

See Section 18.10: Medical management of eye injury.

20.19 POST EXPOSURE PROPHYLAXIS

See Section 10.5: Post-exposure prophylaxis.

20.20 SOFT TISSUE INJURIES

See Primary Health Care STGs and EML; Section 21.3.7: Soft tissue injuries.

20.21 SPRAINS AND STRAINS

See Primary Health Care STGs and EML; Section 21.3.8: Sprains and strains.

References:

[i] Cardiac pulmonary arrest – COVID-19 considerations: Resuscitation Council of South Africa. Advanced Cardiac Arrest Algorithm for Suspected Communicable Disease (Respiratory), 2021. https://resus.co.za/

Cardiac pulmonary arrest – COVID-19 considerations: Atkins DL, Sasson C, Hsu A, Aziz K, Becker LB, Berg RA, et al.; Emergency Cardiovascular Care Committee and Get With the Guidelines-Resuscitation, Adult and Pediatric Task Forces of the American Heart Association in Collaboration With the American Academy of Pediatrics, American Association for Respiratory Care, American Society of Anesthesiologists, and the Society of Critical Care Anesthesiologists. 2022 Interim Guidance to Health Care Providers for Basic and Advanced Cardiac Life Support in Adults, Children, and Neonates With Suspected or Confirmed COVID-19: From the Emergency Cardiovascular Care Committee and Get With The Guidelines-Resuscitation Adult and Pediatric Task Forces of the American Heart Association in Collaboration With the American Academy of Pediatrics, American Association for Respiratory Care, the Society of Critical Care Anesthesiologists, and American Society of Anesthesiologists. Circ Cardiovasc Qual Outcomes. 2022 Apr;15(4):e008900. https://pubmed.ncbi.nlm.nih.gov/35072519/

[ii] Cardiac pulmonary arrest – COVID-19 considerations & PPE: Brown A, Schwarcz L, Counts CR, Barnard LM, Yang BY, Emert JM, et al. Risk for Acquiring Coronavirus Disease Illness among Emergency Medical Service Personnel Exposed to Aerosol-Generating Procedures. Emerg Infect Dis. 2021 Sep;27(9):2340-2348. https://pubmed.ncbi.nlm.nih.gov/34197282/

[iii] Sodium chloride, 0.9%: Lewis SR, Pritchard MW, Evans DJ, Butler AR, Alderson P, Smith AF, Roberts I. Colloids versus crystalloids for fluid resuscitation in critically ill people. Cochrane Database Syst Rev. 2018 Aug 3;8(8):CD000567. http://www.ncbi.nlm.nih.gov/pubmed/23450531

Sodium chloride, 0.9%: Bunn F, Trivedi D. Colloid solutions for fluid resuscitation. Cochrane Database Syst Rev. 2012 Jul 11;7:CD001319. http://www.ncbi.nlm.nih.gov/pubmed/22786474

Sodium chloride, 0.9%: Mutter TC, Ruth CA, Dart AB. Hydroxyethyl starch (HES) versus other fluid therapies: effects on kidney function. Cochrane Database Syst Rev. 2013 Jul 23;7:CD007594. http://www.ncbi.nlm.nih.gov/pubmed/23881659

Sodium Chloride, 0.9%: National Department of Health, Essential Drugs Programme. Medicine review - Hydroxyethyl Starch (HES) Solutions for acute hypovolaemia due to blood loss (trauma, intraoperative haemorrhage), 6 October 2015. https://www.knowledgehub.org.za/content/standard-treatment-guidelines-and-essential-medicines-list

Sodium chloride 0.9%: National Department of Health: Affordable Medicines, EDP-Adult Hospital level. Medicine Review: Ringer Lactate for resuscitation in adults, updated review, August 2019. https://www.knowledgehub.org.za/content/standard-treatment-guidelines-and-essential-medicines-list

[iv] Sodium chloride 0.9% (cautious bolus administration in CPR): Konstantinides SV, Meyer G, Becattini C, Bueno H, Geersing, G, Harjola V, et al., The Task Force for the diagnosis and management of acute pulmonary embolism of the European Society of Cardiology (ESC). European Respiratory Journal Sep 2019, 54 (3) 1901647. https://pubmed.ncbi.nlm.nih.gov/31473594/

Sodium chloride 0.9% (cautious bolus administration in CPR): Sagristà-Sauleda J, Angel J, Sambola A, Permanyer-Miralda G. Hemodynamic effects of volume expansion in patients with cardiac tamponade. Circulation. 2008 Mar 25;117(12):1545-9. https://pubmed.ncbi.nlm.nih.gov/18332261/

[v] Amiodarone, IV: McLeod SL, Brignardello-Petersen R, Worster A, You J, Iansavichene A, Guyatt G, Cheskes S. Comparative effectiveness of antiarrhythmics for out-of-hospital cardiac arrest: A systematic review and network meta-analysis. Resuscitation. 2017 Dec;121:90-97. https://www.ncbi.nlm.nih.gov/pubmed/29037886

Amiodarone, IV: Chowdhury A, Fernandes B, Melhuish TM, White LD. Antiarrhythmics in Cardiac Arrest: A Systematic Review and Meta-Analysis. Heart Lung Circ. 2018 Mar;27(3):280-290. https://www.ncbi.nlm.nih.gov/pubmed/28988724

Amiodarone, IV: Kudenchuk PJ, Cobb LA, Copass MK, Cummins RO, Doherty AM, Fahrenbruch CE, Hallstrom AP, Murray WA, Olsufka M, Walsh T. Amiodarone for resuscitation after out-of-hospital cardiac arrest due to ventricular fibrillation. N Engl J Med. 1999 Sep 16;341(12):871-8. https://www.ncbi.nlm.nih.gov/pubmed/10486418

Amiodarone, IV: Morrison LJ, Deakin CD, Morley PT, Callaway CW, Kerber RE, Kronick SL, Lavonas EJ, Link MS, Neumar RW, Otto CW, Parr M, Shuster M, Sunde K, Peberdy MA, Tang W, Hoek TL, Böttiger BW, Drajer S, Lim SH, Nolan JP; Advanced Life Support Chapter Collaborators. Part 8: Advanced life support: 2010 International Consensus on Cardiopulmonary Resuscitation and Emergency Cardiovascular Care Science With Treatment Recommendations. Circulation. 2010 Oct 19;122(16 Suppl 2):S345-421. https://www.ncbi.nlm.nih.gov/pubmed/20956256

[vi] Adrenaline (epinephrine), intra-osseous: Resuscitation Council of Southern Africa: Advanced cardiac arrest algorithm, 2015. www.resuscitationcouncil.co.za

[vii] Asystole >20 minutes (termination of resuscitation): 2020 American Heart Association. 2020 American Heart Association Guidelines for CPR and ECC https://cpr.heart.org/en/resuscitation-science/cpr-and-ecc-guidelines

Asystole >20 minutes (termination of resuscitation): Ebell MH, Vellinga A, Masterson S, Yun P. Meta-analysis of the accuracy of termination of resuscitation rules for out-of-hospital cardiac arrest. Emerg Med J. 2019 Aug;36(8):479-484. https://pubmed.ncbi.nlm.nih.gov/31142552/

Asystole >20 minutes (termination of resuscitation): Lin YY, Lai YY, Chang HC, Lu CH, Chiu PW, Kuo YS, Huang SP, et al. Predictive performances of ALS and BLS termination of resuscitation rules in out-of-hospital cardiac arrest for different resuscitation protocols. BMC Emerg Med. 2022 Mar 27;22(1):53. https://pubmed.ncbi.nlm.nih.gov/35346055/

[viii] Blood glucose control: Clifton W. Callaway, Michael W. Donnino, Ericka L. Fink, Romergryko G. Geocadin, Eyal Golan, Karl B. Kern, Marion Leary, William J. Meurer, Mary Ann Peberdy, Trevonne M. Thompson, Janice L. Zimmerman. 2015 American Heart Association Guidelines Update for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care. Part 8: Post–Cardiac Arrest Care. Circulation. 2015;132:S465-S482. https://www.ncbi.nlm.nih.gov/pubmed/26472996

[ix] Temperature control: Dankiewicz J, Cronberg T, Lilja G, Jakobsen JC, Levin H, Ullén S, et al; TTM2 Trial Investigators. Hypothermia versus Normothermia after Out-of-Hospital Cardiac Arrest. N Engl J Med. 2021 Jun 17;384(24):2283-2294. https://pubmed.ncbi.nlm.nih.gov/34133859/

[x] Anticoagulants (deep vein prophylaxis): Dentali F, Douketis JD, Gianni M, Lim W, Crowther MA. Meta-analysis: anticoagulant prophylaxis to prevent symptomatic venous thromboembolism in hospitalized medical patients. Ann Intern Med. 2007;146(4):278. https://www.ncbi.nlm.nih.gov/pubmed/17310052

[xi] Dextrose 50%, IV: Moore C, Woollard M. Dextrose 10% or 50% in the treatment of hypoglycaemia out of hospital? A randomised controlled trial. Emerg Med J. 2005 Jul;22(7):512-5. https://pubmed.ncbi.nlm.nih.gov/15983093/

Dextrose 50%, IV: The Society for Endocrinology, Metabolism and Diabetes of South Africa Type 2 Diabetes Guidelines Expert Committee. The 2017 SEMDSA Guideline for the Management of Type 2 Diabetes Guideline Committee. JEMDSA 2017; 21(1)(Supplement 1): S1-S196.
http://www.jemdsa.co.za/index.php/JEMDSA/article/view/647/937

[xii] Sodium chloride 0.9% (cautious bolus administration in post cardiac arrest): Konstantinides SV, Meyer G, Becattini C, Bueno H, Geersing, G, Harjola V, et al., The Task Force for the diagnosis and management of acute pulmonary embolism of the European Society of Cardiology (ESC). European Respiratory Journal Sep 2019, 54 (3) 1901647. https://pubmed.ncbi.nlm.nih.gov/31473594/

Sodium chloride 0.9% (cautious bolus administration in post cardiac arrest): Sagristà-Sauleda J, Angel J, Sambola A, Permanyer-Miralda G. Hemodynamic effects of volume expansion in patients with cardiac tamponade. Circulation. 2008 Mar 25;117(12):1545-9. https://pubmed.ncbi.nlm.nih.gov/18332261/

[xiii] Adrenaline (epinephrine): Clifton W. Callaway, Michael W. Donnino, Ericka L. Fink, Romergryko G. Geocadin, Eyal Golan, Karl B. Kern, Marion Leary, William J. Meurer, Mary Ann Peberdy, Trevonne M. Thompson, Janice L. Zimmerman. 2015 American Heart Association Guidelines Update for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care. Part 8: Post–Cardiac Arrest Care. Circulation. 2015;132:S465-S482. https://www.ncbi.nlm.nih.gov/pubmed/26472996

[xiv] Anticonvulsants (seizures): Clifton W. Callaway, Michael W. Donnino, Ericka L. Fink, Romergryko G. Geocadin, Eyal Golan, Karl B. Kern, Marion Leary, William J. Meurer, Mary Ann Peberdy, Trevonne M. Thompson, Janice L. Zimmerman. 2015 American Heart Association Guidelines Update for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care. Part 8: Post–Cardiac Arrest Care. Circulation. 2015;132:S465-S482. https://www.ncbi.nlm.nih.gov/pubmed/26472996

[xv] Paracetamol, oral: Nolan JP, Soar J, Cariou A, Cronberg T, Moulaert VR, Deakin CD, Bottiger BW, Friberg H, Sunde K, Sandroni C. European Resuscitation Council and European Society of Intensive Care Medicine Guidelines for Post-resuscitation Care 2015: Section 5 of the European Resuscitation Council Guidelines for Resuscitation 2015. Resuscitation. 2015 Oct;95:202-222. https://www.ncbi.nlm.nih.gov/pubmed/26477702

Paracetamol, oral: Gebhardt K, Guyette FX, Doshi AA, Callaway CW, Rittenberger JC; Post Cardiac Arrest Service. Prevalence and effect of fever on outcome following resuscitation from cardiac arrest. Resuscitation. 2013 Aug;84(8):1062-7. https://www.ncbi.nlm.nih.gov/pubmed/23619740

[xvi] Promethazine, IM/IV: Shaker MS, Wallace DV, Golden DBK, Oppenheimer J, Bernstein JA, Campbell RL, et al., Anaphylaxis-a 2020 practice parameter update, systematic review, and Grading of Recommendations, Assessment, Development and Evaluation (GRADE) analysis. J Allergy Clin Immunol. 2020 Apr;145(4):1082-1123. https://pubmed.ncbi.nlm.nih.gov/32001253/

[xvii] Hydrocortisone, IV:Shaker MS, Wallace DV, Golden DBK, Oppenheimer J, Bernstein JA, Campbell RL, et al., Anaphylaxis-a 2020 practice parameter update, systematic review, and Grading of Recommendations, Assessment, Development and Evaluation (GRADE) analysis. J Allergy Clin Immunol. 2020 Apr;145(4):1082-1123. https://pubmed.ncbi.nlm.nih.gov/32001253/

[xviii] Fresh frozen plasma: Prematta M, Gibbs JG, Pratt EL, Stoughton TR, Craig TJ. Fresh frozen plasma for the treatment of hereditary angioedema. Ann Allergy Asthma Immunol. 2007 Apr;98(4):383-8.
http://www.ncbi.nlm.nih.gov/pubmed/17458436

Fresh frozen plasma: Hassen GW, Kalantari H, Parraga M, Chirurgi R, Meletiche C, Chan C, Ciarlo J, Gazi F, Lobaito C, Tadayon S, Yemane S, Velez C. Fresh frozen plasma for progressive and refractory angiotensin-converting enzyme inhibitor-induced angioedema. J Emerg Med. 2013 Apr;44(4):764-72. http://www.ncbi.nlm.nih.gov/pubmed/23114109

Fresh frozen plasma: Culley CM, DiBridge JN, Wilson GL Jr. Off-Label Use of Agents for Management of Serious or Life-threatening Angiotensin Converting Enzyme Inhibitor-Induced Angioedema. Ann Pharmacother. 2016 Jan;50(1):47-59. http://www.ncbi.nlm.nih.gov/pubmed/26416949

[xix]Sodium chloride, 0.9%: Lewis SR, Pritchard MW, Evans DJ, Butler AR, Alderson P, Smith AF, Roberts I. Colloids versus crystalloids for fluid resuscitation in critically ill people. Cochrane Database Syst Rev. 2018 Aug 3;8(8):CD000567. http://www.ncbi.nlm.nih.gov/pubmed/23450531

Sodium chloride, 0.9%: Bunn F, Trivedi D. Colloid solutions for fluid resuscitation. Cochrane Database Syst Rev. 2012 Jul 11;7:CD001319. http://www.ncbi.nlm.nih.gov/pubmed/22786474

Sodium chloride, 0.9%: Mutter TC, Ruth CA, Dart AB. Hydroxyethyl starch (HES) versus other fluid therapies: effects on kidney function. Cochrane Database Syst Rev. 2013 Jul 23;7:CD007594. http://www.ncbi.nlm.nih.gov/pubmed/23881659

Sodium Chloride, 0.9%: National Department of Health, Essential Drugs Programme. Medicine review - Hydroxyethyl Starch (HES) Solutions for acute hypovolaemia due to blood loss (trauma, intraoperative haemorrhage), 6 October 2015. https://www.knowledgehub.org.za/content/standard-treatment-guidelines-and-essential-medicines-list

Sodium chloride 0.9%: National Department of Health: Affordable Medicines, EDP-Adult Hospital level. Medicine Review: Ringer Lactate for resuscitation in adults, updated review, August 2019. https://www.knowledgehub.org.za/content/standard-treatment-guidelines-and-essential-medicines-list

[xx] Oxygen (medically ill patients): National Department of Health. Affordable Medicines, EDP-Primary Healthcare and Adult Hospital Level. Evidence summary – oxygen therapy in acutely ill patients, 9 September 2021. https://www.knowledgehub.org.za/content/standard-treatment-guidelines-and-essential-medicines-list

Oxygen (medically ill patients): Chu DK, Kim LH, Young PJ, Zamiri N, Almenawer SA, Jaeschke R, Szczeklik W, Schünemann HJ, Neary JD, Alhazzani W. Mortality and morbidity in acutely ill adults treated with liberal versus conservative oxygen therapy (IOTA): a systematic review and meta-analysis. Lancet. 2018 Apr 28;391(10131):1693-1705. https://www.ncbi.nlm.nih.gov/pubmed/29726345

Oxygen (medically ill patients): Siemieniuk RAC, Chu DK, Kim LH, Güell-Rous MR, Alhazzani W, Soccal PM, et al. Oxygen therapy for acutely ill medical patients: a clinical practice guideline. BMJ. 2018 Oct 24;363:k4169. https://pubmed.ncbi.nlm.nih.gov/30355567/

Oxygen (medically ill patients): Alves M, Prada L, Costa J, Ferreira JJ, Pinto FJ, Caldeira D. Effect of oxygen supply on mortality in acute ST-elevation myocardial infarction: systematic review and meta-analysis. Eur J Emerg Med. 2021 Jan 1;28(1):11-18. https://pubmed.ncbi.nlm.nih.gov/33079738/

[xxi] Salbutamol nebulisation (anaphylaxis): Resuscitation Council of Southern Africa: Emergency management of anaphylaxis algorithm, 2015/16. www.resuscitationcouncil.co.za

[xxii] Ipratropium nebulisation (anaphylaxis): Resuscitation Council of Southern Africa: Emergency management of anaphylaxis algorithm, 2015/16. www.resuscitationcouncil.co.za

[xxiii] Promethazine, IV/ cetirizine, oral: Sheikh A, ten Broek Vm, Brown SG, Simons FE. H1-antihistamines for the treatment of anaphylaxis with and without shock. Cochrane Database Syst Rev. 2007 Jan 24;(1):CD006160. https://www.ncbi.nlm.nih.gov/pubmed/17253584

Promethazine, IV/ cetirizine, oral: Resuscitation Council of South Africa, Emergency Management of Anaphylaxis Guidelines, 2015. https://resus.co.za/anaphylaxis/

Promethazine, IV/ cetirizine, oral: Fernando SL, Broadfoot AJ. Ondansetron anaphylaxis: a case report and protocol for skin testing. Br J Anaesth. 2009 Feb;102(2):285-6. https://www.ncbi.nlm.nih.gov/pubmed/19151059

[xxiv] Olanzapine, oral/oral dispersible tablet/IM/: National Department of Health: Affordable Medicines, EDP-Adult Hospital level. Medicine Review: Olanzapine for delirium, 9 August 2022. https://www.knowledgehub.org.za/content/standard-treatment-guidelines-and-essential-medicines-list

Olanzapine, oral /oral dispersible tablet/IM: Taylor, David; Paton, Carol; Kapur, Shitij. The Maudsley Prescribing Guidelines, Thirteenth Edition. West Sussex: John Wiley & Sons Ltd; 2019.

NICE CG103: Delirium: prevention, diagnosis and management in hospital and long-term care https://www.nice.org.uk/guidance/cg103.

[xxv] Benzodiazepine (dosing): Taylor, David; Paton, Carol; Kapur, Shitij. The Maudsley Prescribing Guidelines, Thirteenth Edition. West Sussex: John Wiley & Sons Ltd; 2019

Benzodiazepine (dosing): South African Medicines Formulary. 14th Edition. Division of Clinical Pharmacology. University of Cape Town, 2022.

[xxvi] Benzodiazepines (dose in the elderly): Taylor, David; Paton, Carol; Kapur, Shitij. The Maudsley Prescribing Guidelines, Thirteenth Edition. West Sussex: John Wiley & Sons Ltd; 2019

Benzodiazepines (dose in the elderly): South African Medicines Formulary. 14th Edition. Division of Clinical Pharmacology. University of Cape Town, 2022.

[xxvii] Thiamine (alcohol withdrawal/ Wernicke's encephalopathy): Ambrose ML, Bowden SC, Whelan G. Thiamin treatment and working memory function of alcohol-dependent people: preliminary findings. Alcohol Clin Exp Res. 2001 Jan;25(1):112-6. https://pubmed.ncbi.nlm.nih.gov/11198705/

Thiamine (alcohol withdrawal/ Wernicke's encephalopathy): Day E, Bentham PW, Callaghan R, Kuruvilla T, George S. Thiamine for prevention and treatment of Wernicke-Korsakoff Syndrome in people who abuse alcohol. Cochrane Database Syst Rev. 2013 Jul 1;2013(7):CD004033. https://pubmed.ncbi.nlm.nih.gov/23818100

Thiamine (alcohol withdrawal/ Wernicke's encephalopathy): Thomson AD, Cook CC, Touquet R, Henry JA; Royal College of Physicians, London. The Royal College of Physicians report on alcohol: guidelines for managing Wernicke's encephalopathy in the accident and Emergency Department. Alcohol Alcohol. 2002 Nov-Dec;37(6):513-21. Erratum in: Alcohol Alcohol. 2003 May-Jun;38(3):291. https://pubmed.ncbi.nlm.nih.gov/12414541/

[xxviii] Morphine, parenteral (Caution): National Department of Health. Affordable Medicines, EDP-Adult Hospital level. Medicine Review: Morphine for the treatment of acute pulmonary distress, May 2022. https://www.knowledgehub.org.za/content/standard-treatment-guidelines-and-essential-medicines-list

Hendrikse C, Ngah V, Kallon II, Thom G, Leong TD, Cohen K, McCaul M. Signal of harm in morphine use in adults with acute pulmonary oedema: A rapid systematic review. S Afr Med J. 2023 Aug 3;113(8):39-43. doi: 10.7196/SAMJ.2023.v113i8.348. PMID: 37882120.

[xxix] Anaesthetics and sedatives: World Health Organisation. WHO model prescribing information: Drugs used in anaesthesia, 1994. https://apps.who.int/iris/handle/10665/41014

[xxx] Thiopental, IV (contraindication-porphyria): South African Medicines Formulary. 14th Edition. Division of Clinical Pharmacology. University of Cape Town, 2022.

[xxxi] Suxamethonium: Perry JJ, Lee JS, Sillberg VA, Wells GA. Rocuronium versus succinylcholine for rapid sequence induction intubation. Cochrane Database Syst Rev. 2008 Apr 16;(2):CD002788. http://www.ncbi.nlm.nih.gov/pubmed/18425883

[xxxii] Rocuronium: Perry JJ, Lee JS, Sillberg VA, Wells GA. Rocuronium versus succinylcholine for rapid sequence induction intubation. Cochrane Database Syst Rev. 2008 Apr 16;(2):CD002788. http://www.ncbi.nlm.nih.gov/pubmed/18425883

Rocuronium: National Department of Health, Essential Drugs Programme. Medicine review: Rocuronium for muscle relaxation for rapid sequence induction, 31 March 2015. https://www.knowledgehub.org.za/content/standard-treatment-guidelines-and-essential-medicines-list

[xxxiii]Sedation protocols in intensive care: Jackson DL, Proudfoot CW, Cann KF, Walsh T. A systematic review of the impact of sedation practice in the ICU on resource use, costs and patient safety. Crit Care. 2010;14(2):R59. http://www.ncbi.nlm.nih.gov/pubmed/20380720

[xxxiv]Propofol, IV (short-term sedation: second line option): The South African Society of Anaesthesiologists. South African Society of Anaesthesiologists Sedation Guidelines, 2015. South Afr J AnaesthAnalg 2015;21(2)S1-S36.http://www.sasaweb.com/content/images/SAJAA_V21N2_1665_Sedation_Guideline.pdf

Propofol, IV (short-term sedation: second line option): South African Medicines Formulary. 14th Edition. Division of Clinical Pharmacology. University of Cape Town, 2022.

[xxxv] Propofol, IV: Ostermann ME, Keenan SP, Seiferling RA, Sibbald WJ. Sedation in the intensive care unit: a systematic review. JAMA. 2000 Mar 15;283(11):1451-9. http://www.ncbi.nlm.nih.gov/pubmed/10732935

[xxxvi]Ketamine, IV: National Department of Health: Affordable Medicines, EDP-Adult Hospital level. Medicine Review: Ketamine (adjunctive or monotherapy) for analgosedation in traumatised intubated adults on mechanical ventilation,

September 2022. https://www.knowledgehub.org.za/content/standard-treatment-guidelines-and-essential-medicines-list
Hendrikse C, Ngah V, Kallon II, Leong TD, McCaul M. Ketamine as adjunctive or monotherapy for post-intubation sedation in patients with trauma on mechanical ventilation: A rapid review. Afr J Emerg Med. 2023 Dec;13(4):313-321. doi: 10.1016/j.afjem.2023.10.002. Epub 2023 Nov 10. PMID: 38033380; PMCID: PMC10682541.

[xxxvii] Sodium chloride, 0.9%: Lewis SR, Pritchard MW, Evans DJ, Butler AR, Alderson P, Smith AF, Roberts I. Colloids versus crystalloids for fluid resuscitation in critically ill people. Cochrane Database Syst Rev. 2018 Aug 3;8(8):CD000567. http://www.ncbi.nlm.nih.gov/pubmed/23450531

Sodium chloride, 0.9%: Bunn F, Trivedi D. Colloid solutions for fluid resuscitation. Cochrane Database Syst Rev. 2012 Jul 11;7:CD001319. http://www.ncbi.nlm.nih.gov/pubmed/22786474

Sodium chloride, 0.9%: Mutter TC, Ruth CA, Dart AB. Hydroxyethyl starch (HES) versus other fluid therapies: effects on kidney function. Cochrane Database Syst Rev. 2013 Jul 23;7:CD007594. http://www.ncbi.nlm.nih.gov/pubmed/23881659

Sodium Chloride, 0.9%: National Department of Health, Essential Drugs Programme. Medicine review - Hydroxyethyl Starch (HES) Solutions for acute hypovolaemia due to blood loss (trauma, intraoperative haemorrhage), 6 October 2015. https://www.knowledgehub.org.za/content/standard-treatment-guidelines-and-essential-medicines-list

Sodium chloride 0.9%: National Department of Health: Affordable Medicines, EDP-Adult Hospital level. Medicine Review: Ringer Lactate for resuscitation in adults, updated review, August 2019. https://www.knowledgehub.org.za/content/standard-treatment-guidelines-and-essential-medicines-list

[xxxviii] Oxygen (medically ill patients): National Department of Health. Affordable Medicines, EDP-Primary Healthcare and Adult Hospital Level. Evidence summary – oxygen therapy in acutely ill patients, 9 September 2021. https://www.knowledgehub.org.za/content/standard-treatment-guidelines-and-essential-medicines-list

Oxygen (medically ill patients): Chu DK, Kim LH, Young PJ, Zamiri N, Almenawer SA, Jaeschke R, Szczeklik W, Schünemann HJ, Neary JD, Alhazzani W. Mortality and morbidity in acutely ill adults treated with liberal versus conservative oxygen therapy (IOTA): a systematic review and meta-analysis. Lancet. 2018 Apr 28;391(10131):1693-1705. https://www.ncbi.nlm.nih.gov/pubmed/29726345

Oxygen (medically ill patients): Siemieniuk RAC, Chu DK, Kim LH, Güell-Rous MR, Alhazzani W, Soccal PM, et al. Oxygen therapy for acutely ill medical patients: a clinical practice guideline. BMJ. 2018 Oct 24;363:k4169. https://pubmed.ncbi.nlm.nih.gov/30355567/

Oxygen (medically ill patients): Alves M, Prada L, Costa J, Ferreira JJ, Pinto FJ, Caldeira D. Effect of oxygen supply on mortality in acute ST-elevation myocardial infarction: systematic review and meta-analysis. Eur J Emerg Med. 2021 Jan 1;28(1):11-18. https://pubmed.ncbi.nlm.nih.gov/33079738/

[xxxix] Sodium chloride, 0.9%: Lewis SR, Pritchard MW, Evans DJ, Butler AR, Alderson P, Smith AF, Roberts I. Colloids versus crystalloids for fluid resuscitation in critically ill people. Cochrane Database Syst Rev. 2018 Aug 3;8(8):CD000567. http://www.ncbi.nlm.nih.gov/pubmed/23450531

Sodium chloride, 0.9%: Bunn F, Trivedi D. Colloid solutions for fluid resuscitation. Cochrane Database Syst Rev. 2012 Jul 11;7:CD001319. http://www.ncbi.nlm.nih.gov/pubmed/22786474

Sodium chloride, 0.9%: Mutter TC, Ruth CA, Dart AB. Hydroxyethyl starch (HES) versus other fluid therapies: effects on kidney function. Cochrane Database Syst Rev. 2013 Jul 23;7:CD007594. http://www.ncbi.nlm.nih.gov/pubmed/23881659

Sodium Chloride, 0.9%: National Department of Health, Essential Drugs Programme. Medicine review - Hydroxyethyl Starch (HES) Solutions for acute hypovolaemia due to blood loss (trauma, intraoperative haemorrhage), 6 October 2015. https://www.knowledgehub.org.za/content/standard-treatment-guidelines-and-essential-medicines-list

Sodium chloride 0.9%: National Department of Health: Affordable Medicines, EDP-Adult Hospital level. Medicine Review: Ringer Lactate for resuscitation in adults, updated review, August 2019. https://www.knowledgehub.org.za/content/standard-treatment-guidelines-and-essential-medicines-list

[xl] Massive blood transfusion protocol: Groote Schuur Hospital protocol, current.

[xli] Tranexamic acid, IV: CRASH-2 trial collaborators: Shakur H et al. Effects of tranexamic acid on death, vascular occlusive events, and blood transfusion in trauma patients with significant haemorrhage (CRASH-2): a randomised, placebo-controlled trial. Lancet. 2010; 376:23-32. https://www.ncbi.nlm.nih.gov/pubmed/20554319

Tranexamic acid: Roberts I et al. The importance of early treatment with tranexamic acid in bleedingtrauma patients: an exploratory analysis of the CRASH-2 randomised controlled trial. Lancet. 2011; 377:1096-1101.

Tranexamic acid: Ker K, Roberts I, Shakur H, Coats TJ. Antifibrinolytic drugs for acute traumatic injury. Cochrane Database Syst Rev. 2015 May 9;(5):CD004896. https://www.ncbi.nlm.nih.gov/pubmed/25956410

[xlii] Oxygen (medically ill patients): National Department of Health. Affordable Medicines, EDP-Primary Healthcare and Adult Hospital Level. Evidence summary – oxygen therapy in acutely ill patients, 9 September 2021. https://www.knowledgehub.org.za/content/standard-treatment-guidelines-and-essential-medicines-list

Oxygen (medically ill patients): Chu DK, Kim LH, Young PJ, Zamiri N, Almenawer SA, Jaeschke R, Szczeklik W, Schünemann HJ, Neary JD, Alhazzani W. Mortality and morbidity in acutely ill adults treated with liberal versus conservative oxygen therapy (IOTA): a systematic review and meta-analysis. Lancet. 2018 Apr 28;391(10131):1693-1705. https://www.ncbi.nlm.nih.gov/pubmed/29726345

Oxygen (medically ill patients): Siemieniuk RAC, Chu DK, Kim LH, Güell-Rous MR, Alhazzani W, Soccal PM, et al. Oxygen therapy for acutely ill medical patients: a clinical practice guideline. BMJ. 2018 Oct 24;363:k4169. https://pubmed.ncbi.nlm.nih.gov/30355567/

Oxygen (medically ill patients): Alves M, Prada L, Costa J, Ferreira JJ, Pinto FJ, Caldeira D. Effect of oxygen supply on mortality in acute ST-elevation myocardial infarction: systematic review and meta-analysis. Eur J Emerg Med. 2021 Jan 1;28(1):11-18. https://pubmed.ncbi.nlm.nih.gov/33079738/

[xliii] Sodium chloride, 0.9%: Lewis SR, Pritchard MW, Evans DJ, Butler AR, Alderson P, Smith AF, Roberts I. Colloids versus crystalloids for fluid resuscitation in critically ill people. Cochrane Database Syst Rev. 2018 Aug 3;8(8):CD000567. http://www.ncbi.nlm.nih.gov/pubmed/23450531

Sodium chloride, 0.9%: Bunn F, Trivedi D. Colloid solutions for fluid resuscitation. Cochrane Database Syst Rev. 2012 Jul 11;7:CD001319. http://www.ncbi.nlm.nih.gov/pubmed/22786474

Sodium chloride, 0.9%: Mutter TC, Ruth CA, Dart AB. Hydroxyethyl starch (HES) versus other fluid therapies: effects on

kidney function. Cochrane Database Syst Rev. 2013 Jul 23;7:CD007594. http://www.ncbi.nlm.nih.gov/pubmed/23881659

Sodium Chloride, 0.9%: National Department of Health, Essential Drugs Programme. Medicine review - Hydroxyethyl Starch (HES) Solutions for acute hypovolaemia due to blood loss (trauma, intraoperative haemorrhage), 6 October 2015. https://www.knowledgehub.org.za/content/standard-treatment-guidelines-and-essential-medicines-list

Sodium chloride 0.9%: National Department of Health: Affordable Medicines, EDP-Adult Hospital level. Medicine Review: Ringer Lactate for resuscitation in adults, updated review, August 2019. https://www.knowledgehub.org.za/content/standard-treatment-guidelines-and-essential-medicines-list

[xliv] Oxygen (medically ill patients): National Department of Health. Affordable Medicines, EDP-Primary Healthcare and Adult Hospital Level. Evidence summary – oxygen therapy in acutely ill patients, 9 September 2021. https://www.knowledgehub.org.za/content/standard-treatment-guidelines-and-essential-medicines-list

Oxygen (medically ill patients): Chu DK, Kim LH, Young PJ, Zamiri N, Almenawer SA, Jaeschke R, Szczeklik W, Schünemann HJ, Neary JD, Alhazzani W. Mortality and morbidity in acutely ill adults treated with liberal versus conservative oxygen therapy (IOTA): a systematic review and meta-analysis. Lancet. 2018 Apr 28;391(10131):1693-1705. https://www.ncbi.nlm.nih.gov/pubmed/29726345

Oxygen (medically ill patients): Siemieniuk RAC, Chu DK, Kim LH, Güell-Rous MR, Alhazzani W, Soccal PM, et al. Oxygen therapy for acutely ill medical patients: a clinical practice guideline. BMJ. 2018 Oct 24;363:k4169. https://pubmed.ncbi.nlm.nih.gov/30355567/

Oxygen (medically ill patients): Alves M, Prada L, Costa J, Ferreira JJ, Pinto FJ, Caldeira D. Effect of oxygen supply on mortality in acute ST-elevation myocardial infarction: systematic review and meta-analysis. Eur J Emerg Med. 2021 Jan 1;28(1):11-18. https://pubmed.ncbi.nlm.nih.gov/33079738/

[xlv]Ceftriaxone, IV: Gaieski DF, Mikkelsen ME, Band RA, Pines JM, Massone R, Furia FF, Shofer FS, Goyal M. Impact of time to antibiotics on survival in patients with severe sepsis or septic shock in whom early goal-directed therapy was initiated in the emergency department. Crit Care Med. 2010 Apr;38(4):1045-53. http://www.ncbi.nlm.nih.gov/pubmed/20048677

Ceftriaxone, IV: Dellinger RP, Levy MM, Rhodes A, Annane D, Gerlach H, Opal SM, Sevransky JE, Sprung CL, Douglas IS, Jaeschke R, Osborn TM, Nunnally ME, Townsend SR, Reinhart K, Kleinpell RM, Angus DC, Deutschman CS, Machado FR, Rubenfeld GD, Webb SA, Beale RJ, Vincent JL, Moreno R; Surviving Sepsis Campaign Guidelines Committee including the Pediatric Subgroup. Surviving sepsis campaign: international guidelines for management of severe sepsis and septic shock: 2012. Crit Care Med. 2013 Feb;41(2):580-637. http://www.ncbi.nlm.nih.gov/pubmed/23353941

[xlvi] Ringer Lactate, IV: National Department of Health: Affordable Medicines, EDP-Adult Hospital level. Medicine Review: Ringer Lactate for resuscitation in adults, updated review, August 2019. https://www.knowledgehub.org.za/content/standard-treatment-guidelines-and-essential-medicines-list

Ringer Lactate, IV: Antequera Martin AM, Barea Mendoza JA, Muriel A, Saez I, Chico-Fernandez M, Estrada-Lorenzo JM, et al. Buffered solutions versus 0.9% saline for resuscitation in critically ill adults and children. Cochrane Database Syst Rev. 2019 Jul 19;7:CD012247. https://www.ncbi.nlm.nih.gov/pubmed/31334842

Ringer Lactate, IV: Liu C, Lu G, Wang D, Lei Y, Mao Z, Hu P, Hu J, Liu R, Han D, Zhou F. Balanced crystalloids versus normal saline for fluid resuscitation in critically ill patients: A systematic review and meta-analysis with trial sequential analysis. Am J Emerg Med. 2019 Mar 1. pii: S0735-6757(19)30149-4. https://www.ncbi.nlm.nih.gov/pubmed/3085204

Ringer Lactate, IV: Brown RM, Wang L, Coston TD, Krishnan NI, Casey JD, Wanderer JP, Ehrenfeld JM, Byrne DW, Stollings JL, Siew ED, Bernard GR, Self WH, Rice
TW, Semler MW; SMART Investigators and the Pragmatic Critical Care Research Group. Balanced Crystalloids Versus Saline in Sepsis: A Secondary Analysis of the SMART Trial. Am J Respir Crit Care Med. 2019 Aug 27. https://www.ncbi.nlm.nih.gov/pubmed/31454263

Ringer Lactate, IV: Rochwerg B, Alhazzani W, Sindi A, Heels-Ansdell D, Thabane L, Fox-Robichaud A, et al. Fluid resuscitation in sepsis: A systematic review and network meta-analysis. Ann Intern Med. 2014;161(5):347–55. https://www.ncbi.nlm.nih.gov/pubmed/250474

[xlvii]Oxygen (medically ill patients): National Department of Health. Affordable Medicines, EDP-Primary Healthcare and Adult Hospital Level. Evidence summary – oxygen therapy in acutely ill patients, 9 September 2021. https://www.knowledgehub.org.za/content/standard-treatment-guidelines-and-essential-medicines-list Oxygen (medically ill patients): Chu DK, Kim LH, Young PJ, Zamiri N, Almenawer SA, Jaeschke R, Szczeklik W, Schünemann HJ, Neary JD, Alhazzani W. Mortality and morbidity in acutely ill adults treated with liberal versus conservative oxygen therapy (IOTA): a systematic review and meta-analysis. Lancet. 2018 Apr 28;391(10131):1693-1705. https://www.ncbi.nlm.nih.gov/pubmed/29726345

Oxygen (medically ill patients): Siemieniuk RAC, Chu DK, Kim LH, Güell-Rous MR, Alhazzani W, Soccal PM, et al. Oxygen therapy for acutely ill medical patients: a clinical practice guideline. BMJ. 2018 Oct 24;363:k4169. https://pubmed.ncbi.nlm.nih.gov/30355567/

Oxygen (medically ill patients): Alves M, Prada L, Costa J, Ferreira JJ, Pinto FJ, Caldeira D. Effect of oxygen supply on mortality in acute ST-elevation myocardial infarction: systematic review and meta-analysis. Eur J Emerg Med. 2021 Jan 1;28(1):11-18. https://pubmed.ncbi.nlm.nih.gov/33079738/

[xlviii]Sodium chloride, 0.9%: Lewis SR, Pritchard MW, Evans DJ, Butler AR, Alderson P, Smith AF, Roberts I. Colloids versus crystalloids for fluid resuscitation in critically ill people. Cochrane Database Syst Rev. 2018 Aug 3;8(8):CD000567. http://www.ncbi.nlm.nih.gov/pubmed/23450531

Sodium chloride, 0.9%: Bunn F, Trivedi D. Colloid solutions for fluid resuscitation. Cochrane Database Syst Rev. 2012 Jul 11;7:CD001319. http://www.ncbi.nlm.nih.gov/pubmed/22786474

Sodium chloride, 0.9%: Mutter TC, Ruth CA, Dart AB. Hydroxyethyl starch (HES) versus other fluid therapies: effects on kidney function. Cochrane Database Syst Rev. 2013 Jul 23;7:CD007594. http://www.ncbi.nlm.nih.gov/pubmed/23881659

Sodium Chloride, 0.9%: National Department of Health, Essential Drugs Programme. Medicine review - Hydroxyethyl Starch (HES) Solutions for acute hypovolaemia due to blood loss (trauma, intraoperative haemorrhage), 6 October 2015. https://www.knowledgehub.org.za/content/standard-treatment-guidelines-and-essential-medicines-list

Sodium chloride 0.9%: National Department of Health: Affordable Medicines, EDP-Adult Hospital level. Medicine

Review: Ringer Lactate for resuscitation in adults, updated review, August 2019. https://www.knowledgehub.org.za/content/standard-treatment-guidelines-and-essential-medicines-list

[xlix] Dobutamine: MCC registered South African package insert: Pharmaplan Cardiject® powder for IV infusion, 250 mg/vial.

[l] Sodium chloride, 0.9%: Lewis SR, Pritchard MW, Evans DJ, Butler AR, Alderson P, Smith AF, Roberts I. Colloids versus crystalloids for fluid resuscitation in critically ill people. Cochrane Database Syst Rev. 2018 Aug 3;8(8):CD000567. http://www.ncbi.nlm.nih.gov/pubmed/23450531

Sodium chloride, 0.9%: Bunn F, Trivedi D. Colloid solutions for fluid resuscitation. Cochrane Database Syst Rev. 2012 Jul 11;7:CD001319. http://www.ncbi.nlm.nih.gov/pubmed/22786474

Sodium chloride, 0.9%: Mutter TC, Ruth CA, Dart AB. Hydroxyethyl starch (HES) versus other fluid therapies: effects on kidney function. Cochrane Database Syst Rev. 2013 Jul 23;7:CD007594. http://www.ncbi.nlm.nih.gov/pubmed/23881659

Sodium Chloride, 0.9%: National Department of Health, Essential Drugs Programme. Medicine review - Hydroxyethyl Starch (HES) Solutions for acute hypovolaemia due to blood loss (trauma, intraoperative haemorrhage), 6 October 2015. https://www.knowledgehub.org.za/content/standard-treatment-guidelines-and-essential-medicines-list

Sodium chloride 0.9%: National Department of Health: Affordable Medicines, EDP-Adult Hospital level. Medicine Review: Ringer Lactate for resuscitation in adults, updated review, August 2019. https://www.knowledgehub.org.za/content/standard-treatment-guidelines-and-essential-medicines-list

CHAPTER 21
ONCOLOGIC EMERGENCIES

21.1 ONCOLOGICAL EMERGENCIES

Any acute, potentially morbid or life-threatening event directly or indirectly related to a patient's tumour or its treatment. Most oncological emergencies can be classified as metabolic, haematologic, structural, or side effects of chemotherapy agents or radiation therapy.

21.1.1 METABOLIC EMERGENCIES

21.1.1.1 HYPERCALCAEMIA OF MALIGNANCY

See section 8.9: Hypercalcaemia, including primary hyperparathyroidism

21.1.1.2 SYNDROME OF INAPPROPRIATE ANTIDIURETIC HORMONE (SIADH)

E22.2

DESCRIPTION

Patients present with: anorexia, nausea, vomiting, constipation, muscle weakness, myalgia, polyuria, polydipsia, neurologic symptoms (e.g. seizures, coma).

For management see section: 7.2.4:Hyponatraemia.

REFERRAL

Refer to Oncology Unit for management of underlying malignancy producing Antiduretic Hormone (ADH).

21.1.1.3 TUMOUR LYSIS SYNDROME

E88.3

DESCRIPTION

Rapid destruction of malignant cells can result in the release of cellular breakdown products and intracellular ions, causing potentially lethal metabolic derangements including acute renal failure.
Commonly seen in cancers with rapidly growing tumours and high tumour burdens, particularly acute leukaemias, chronic myeloid leukaemia and high-grade lymphoma, generally following chemotherapy.

Presentation: (Cairo-Bishop definition)

» azotaemia
» acidosis
» hyperphosphataemia >1.45 mmol/L
» hyperkalaemia >6.0 mmol/L
» hypocalcaemia <1.75 mmol/L

» uric acid >0.476 mmol/L

GENERAL MEASURES

There is an increased risk of arrhythmias.
Monitor urine output.
Monitor urine and electrolytes, creatinine and uric acid levels.

MEDICINE TREATMENT

Fluid resuscitation:

» IV hydration 2–3 L/m^2/day. The urine output needs to be monitored and maintained within 80–100 mL/m^2/hour.
» Diuretics are not indicated in patients with normal renal and cardiac function; and are contraindicated in patients with hypovolemia.

- Sodium chloride 0.9%, IV, 1000 mL 6–8 hourly.

If patient is hypernatraemic or fluid overloaded, consult a specialist.

LoE:III[i]

For control of uric acid:

- Allopurinol, oral, 100 mg 8 hourly.
  - Maximum dose: 300 mg 8 hourly.
  - Adjust dose to 50 mg 8 hourly, if eGFR <20 mL/minute.

LoE:III[ii]

Correct electrolyte imbalances:

» For hyperkalaemia, see section 7.2.1: Hyperkalaemia.
» For hypocalcaemia see section 8.10 Hypocalcaemia.

REFERRAL

Transfer to oncology unit.

21.1.2 HAEMATOLOGIC EMERGENCIES

21.1.2.1 FEBRILE NEUTROPENIA

See section 2.2: Febrile neutropenia.

21.1.2.2 HYPERVISCOSITY AND LEUCOSTATIC SYNDROMES

D78.9

DESCRIPTION

Hyperviscosity is seen in patients with Waldenström's macroglobulinemia and multiple myeloma, while leucostasis may be seen in patients with acute leukaemias and chronic myeloid leukaemia with high white cell counts. Sludging and decreased perfusion of the microvasculature and vascular stasis occur due to increased paraproteins or leucostasis.
Patients present with spontaneous bleeding, visual signs and symptoms, and

neurologic defects.

GENERAL MEASURES
Perform investigations: FBC, peripheral blood smear, serum protein electrophoresis (SPEP) and erythrocyte sedimentation rate (ESR).
Monitor urine, electrolytes and creatinine.

REFERRAL
Ensure adequate hydration and refer.

21.1.3 STRUCTURAL EMERGENCIES

21.1.3.1 EPIDURAL SPINAL CORD COMPRESSION
G95.2

DESCRIPTION
Seen in breast, lung, and prostate cancers, as well as multiple myeloma.
Patients present with new back pain that worsens when lying down, late paraparesis, late incontinence, and loss of sensory function.

GENERAL MEASURES
To evaluate level of neurologic function, perform a spinal x-ray or MRI if available.

MEDICINE TREATMENT
- Dexamethasone, IV, 16 mg immediately as a single dose.
  - Followed by 4 mg 6 hourly, until transfer.

LoE:III[iii]

REFERRAL
Urgent referral to tertiary services with oncology or neurosurgery services.

21.1.3.2 MALIGNANT PERICARDIAL EFFUSION
I31.3

DESCRIPTION
Seen in metastatic lung and breast cancer, melanoma, leukaemia, and lymphoma.
Patients present with dyspnoea, fatigue, distended neck veins, distant heart sounds, tachycardia, orthopnoea, narrow pulse pressure, pulsus paradoxus, or water-bottle heart.

Investigation
Trans-thoracic echocardiography.

GENERAL MEASURES
Management is dependent on the underlying aetiology and symptom progression.
Diagnostic and therapeutic pericardiocentesis:
» Immediate pericardiocentesis is mandatory for patients with tamponade.
» Send some of the fluid drained for microbiology and cytology.

REFERRAL
All patients for definitive therapy.

21.1.3.3 SUPERIOR VENA CAVA SYNDROME
I87.1

DESCRIPTION
Superior Vena Cava (SVC) obstruction may be seen in lung cancer, germ cell tumours, lymphomas, thyroid carcinomas, and metastatic mediastinal tumours. Indwelling central venous catheters may cause SVC syndrome due to venous thrombosis.
Patients present with: cough, dyspnea, dysphagia, facial oedema, or upper extremity swelling or discoloration, with development of collateral venous circulation.

GENERAL MEASURES
Histological diagnosis is essential for definitive management.
Head elevation and supplementary oxygen.

MEDICINE TREATMENT
Maintain normovolaemia.
- Sodium chloride 0.9%, IV, 1000 mL 8 hourly.
- Corticosteroids may be considered in consultation with a specialist.

REFERRAL
Refer for histological diagnosis, and further management.

21.2 SIDE EFFECTS FROM ONCOLOGY TREATMENT AGENT

21.2.1 DIARRHOEA
Refer to section 1.3.3: Diarrhoea, acute non-inflammatory.

21.2.2 EXTRAVASATIONS

T80.8

DESCRIPTION

Chemotherapeutic agents are classified as vesicants (can cause necrosis), non-vesicants, and irritants.
Patients present with pain and erythema at infusion site, swelling, necrosis, contractures.

GENERAL MEASURES

Limb elevation.

MEDICINE TREATMENT

Long term

Small localised area of erythema at the catheter insertion site will usually resolve without antibiotic therapy.

In patients with larger areas of erythema and tenderness extending beyond the insertion site, where secondary infection is suspected:

- Clindamycin, oral, 450 mg 8 hourly for 5 days. *LoE:III*[iv]

Catheter related infections

If patients with peripheral or central venous catheter infections are systemically unwell they should be treated as a venous catheter-related systemic blood infection.
Microbiologic specimen (for speciation and sensitivity).

REFERRAL

All patients to oncological department where chemotherapy was administered.

21.2.3 CONSTIPATION

See section 24.1.2: Constipation.

21.3 SIDE EFFECTS FROM RADIATION AND CHEMOTHERAPY

21.3.1 RADIATION AND CHEMOTHERAPY RELATED MUCOSITIS

K12.3

DESCRIPTION

An inflammatory reaction where shallow ulcerative lesions occur on mucosal surfaces.

GENERAL MEASURES

Avoid irritants (e.g.: smoke, alcohol and hot spicy food).
Ensure adequate fluid intake e.g.: 2 L/day.
Modify diet to include soft or pureed foods.
Use lip care e.g. petroleum jelly, as required.
Keep dentures clean and snug fitting. If loose, refer to dentist.
Ensure adequate mouth care:

» Clean teeth with soft toothbrush or clean cloth.
» Avoid dental flossing.
» Rinse and gargle regularly, at a minimum after every meal.

Simple mouth rinse:

- ½ teaspoon salt
- 3 teaspoons sodium bicarbonate
- 1 L of filtered or previously boiled water.
  (Discard this mixture after 3 days).

LoE:III^{v}

MEDICINE TREATMENT

Adequate pain control. See section 25.2: Analgesia for acute non-surgical pain.

21.3.2 WET DESQUAMATION OF SKIN

R23.4

DESCRIPTION

Acute toxicity of skin that occurs during radiation treatment and up to 2-3 weeks after completion of the radiation.
Few or even no skin care products are effective to prevent or reduce acute radiotherapy skin reactions.

GENERAL MEASURES

Keep skin clean and apply paraffin gauze dressings daily.
Avoid friction and trauma from clothes, weather, etc.
Prevent infection.
Encourage good nutrition.
Encourage smoking cessation.

MEDICINE TREATMENT

Adequate pain control. See section 25.2: Analgesia for acute non-surgical pain.

21.3.3 RADIATION- OR CHEMOTHERAPY-INDUCED PNEUMONITIS

J70.0

DESCRIPTION

Radiation pneumonitis is inflammation of the lung caused by radiation therapy to the chest. It mostly develops 1–6 months after treatment.
Chemotherapy-induced pneumonitis is inflammation of the lung caused by various chemotherapy agents. It mostly develops on treatment.
Symptoms include: fever, dry cough, chest congestion, shortness of breath, and chest pain.
The differential diagnosis includes infectious pneumonitis, pulmonary embolism, and tumor recurrence.

GENERAL MEASURES

Symptoms generally resolve within 7–10 days following cessation of treatment.
Maintain hydration.

MEDICINE TREATMENT

For symptomatic subacute pneumonitis:

- Corticosteroids (intermediate-acting) e.g.:
- Prednisone 1 mg/kg daily for 2–4 weeks at a maximum daily dose of 40–60 mg, and then taper slowly over 3–12 weeks. Refer to Appendix II for an example of a dose reduction regimen. *LoE:III*[M]

REFERRAL

All patients with symptomatic pneumonitis.

21.3.4 RADIATION PROCTITIS

K62.7

DESCRIPTION

An inflammatory process of the rectal mucosa that can present acutely (immediately after the initiation of radiation therapy or up to 3 months after) or chronically (8-12 months after completion of therapy). The acute process is usually self-limiting.

Symptoms include diarrhoea, nausea, cramps, tenesmus, urgency, mucus discharge, and minor bleeding.
Severe complications include bleeding, strictures, perforation, fistula, and bowel obstruction.

Diagnosis
Suspect radiation proctitis when there has been previous radiation to the pelvis.
On colonoscopy/sigmoidoscopy, pallor, friability, telangiectasia are seen localised to the area that was exposed to radiation. Do not biopsy.
Exclude other causes, e.g.: malignancy, infection, or inflammatory bowel disease.

REFERRAL
All patients to a radiation oncology centre.

21.3.5 RADIATION- OR CHEMOTHERAPY-INDUCED CYSTITIS
N30.4

DESCRIPTION
Symptoms include dysuria, frequency, nocturia, recurrent haematuria, and recurrent urinary tract infection.

GENERAL MEASURES
Increase fluid intake.
Urine microscopy, culture and sensitivity to exclude/confirm an infection.
High dose cyclophosphamide and ifosfamide may cause severe cystitis due to excretion of acrolein into bladder.
Acute cystitis is usually self-limiting and resolves in one to two weeks after completing radiation therapy. If symptoms continue, cystoscopy with biopsy is indicated.

REFERRAL
All patients.

21.4 SIDE EFFECT FROM CHRONIC PAIN MEDICATION

21.4.1 CONSTIPATION
See section 25.1.3: Treatment of adverse effects of chronic opioid use.

21.4.2 NAUSEA & VOMITING
See section 25.1.3: Treatment of adverse effects of chronic opioid use.

21.4.3 DEPRESSION
See section 24.2.3: Depression.

References:

[i] Sodium Chloride 0.9%, IV: Coiffier B, Altman A, Pui CH, Younes A, Cairo MS. Guidelines for the management of pediatric and adult tumor lysis syndrome: an evidence-based review. J Clin Oncol. 2008 Jun 1;26(16):2767-78. https://www.ncbi.nlm.nih.gov/pubmed/18509186

[ii] Allopurinol, oral: Krakoff IH. Use of allopurinol in preventing hyperuricemia in leukemia andlymphoma. Cancer. 1966 Nov;19(11):1489-96. https://www.ncbi.nlm.nih.gov/pubmed/5925255

Allopurinol, oral: Coiffier B, Jones GL, Will A, Jackson GH, Webb NJ, Rule S; British Committee for Standards in Haematology. Guidelines for the management of tumour lysis syndrome in adults and children with haematological malignancies on behalf of the British Committee for Standards in Haematology. Br J Haematol. 2015 Jun;169(5):661-71. https://www.ncbi.nlm.nih.gov/pubmed/25876990

Allopurinol, oral: South African Medicines Formulary. 12th Edition. Division of Clinical Pharmacology. University of Cape Town, 2016.

Allopurinol, oral: National Department of Health: Affordable Medicines, EDP-Adult Hospital level. Medicine review: Allopurinol, oral for prevention of tumour lysis syndrome in adults, March 2019. http://www.health.gov.za/

[iii] Dexamethasone, IV: Kumar A, Weber MH, Gokaslan Z, Wolinsky JP, Schmidt M, Rhines L, Fehlings MG, Laufer I, Sciubba DM, Clarke MJ, Sundaresan N, Verlaan JJ, Sahgal A, Chou D, Fisher CG. Metastatic Spinal Cord Compression and Steroid Treatment: A Systematic Review. Clin Spine Surg. 2017 May;30(4):156-163. https://www.ncbi.nlm.nih.gov/pubmed/28437329

Dexamethasone, IV: Greenberg HS, Kim JH, Posner JB. Epidural spinal cord compression from metastatic tumor: results with a new treatment protocol. Ann Neurol. 1980;8:361-366. https://www.ncbi.nlm.nih.gov/pubmed/7436380

Dexamethasone, IV: Vecht CJ, Haaxma-Reiche H, van Putten WL, de Visser M, Vries EP, Twijnstra A. Initial bolus of conventional versus high-dose dexamethasone in metastatic spinal cord compression. Neurology. 1989 Sep;39(9):1255-7. https://www.ncbi.nlm.nih.gov/pubmed/2771077

Dexamethasone, IV: National Department of Health: Affordable Medicines, EDP-Adult Hospital level. Historically accepted use-review: Dexamethasone IV for metastatic spinal cord compression, March 2019. http://www.health.gov.za/

Dexamethasone, IV (dosing): National Institute for Health and Care Excellence. Clinical Guidelines: Metastatic spinal cord compression in adults: risk assessment, diagnosis and management, November 2008. https://www.nice.org.uk/guidance/cg75

[iv] Clindamycin, oral: South African Antibiotic Stewardship Programme. A Pocket Guide to Antibiotic Prescribing for Adults in South Africa, 2015.http://www.fidssa.co.za/images/SAASP_Antibiotic_Gudidelines_2015.pdf

Clindamycin, oral: South African Medicines Formulary. 12th Edition. Division of Clinical Pharmacology. University of Cape Town, 2016.

Clindamycin, oral: Bouazza N, Pestre V, Jullien V, Curis E, Urien S, Salmon D, Tréluyer JM. Population pharmacokinetics of clindamycin orally and intravenously administered in patients with osteomyelitis. Br J ClinPharmacol. 2012 Dec;74(6):971-7.http://www.ncbi.nlm.nih.gov/pubmed/22486719

[v] Saline mouth rinse: Huang BS, Wu SC, Lin CY, Fan KH, Chang JT, Chen SC. The effectiveness of a saline mouth rinse regimen and education programme on radiation-induced oral mucositis and quality of life in oral cavity cancer patients: A randomised controlled trial. Eur J Cancer Care (Engl). 2018 Mar;27(2):e12819. https://www.ncbi.nlm.nih.gov/pubmed/29315944

[vi] Prednisone, oral: Small W Jr, Woloschak G. Radiation toxicity: a practical guide. Introduction. Cancer Treat Res. 2006;128:3-5. https://www.ncbi.nlm.nih.gov/pubmed/16335011

Prednisone, oral: Ta V, Aronowitz P. Radiation pneumonitis. J Gen Intern Med. 2011 Oct;26(10):1213-4. https://www.ncbi.nlm.nih.gov/pubmed/21538170

Prednisone, oral: Conway JL, Long K, Ploquin N, Olivotto IA. Unexpected Symptomatic Pneumonitis Following Breast Tangent Radiation: A Case Report. Cureus. 2015 Oct 22;7(10):e363. https://www.ncbi.nlm.nih.gov/pubmed/26623218

Prednisone, oral: National Department of Health: Affordable Medicines, EDP-Adult Hospital level. Medicine Review: Prednisone, oral for radiation pneumonitis in Adults, November 2019. http://www.health.gov.za/

CHAPTER 22
MEDICINES USED FOR DIAGNOSIS

22.1 DIAGNOSTIC CONTRAST AGENTS AND RELATED SUBSTANCES

Medication used in diagnostic radiology includes:
Barium sulphate suspension.

- Non-ionic contrast media, e.g.:
  - iohexol, or
  - iopamidol, or
  - iopromide, or
  - ioversol.

SAFETY
The overall rate of adverse reactions is estimated to be less than 1 in 100[i] when using non-ionic contrast media and serious allergic reactions are even less common (about 1 in 2000[ii]). Contrast media-associated fatality is rare, estimated to be 2 per million injections.[iii]

Management of any reaction depends on it's severity. Life-threatening acute cardiopulmonary collapse should be treated according to guidelines for cardiopulmonary resuscitation. See chapter 20: Emergencies and injuries. Moderate and severe reactions may be associated with bronchospasm and wheeze, stridor, hypotension, and loss of consciousness. Stop the infusion of the contrast agent and start treatment as for anaphylaxis including adrenaline (epinephrine), oxygen (if indicated), intravenous fluids, and antihistamines. See sections 20.6: Angioedema and 20.7: Anaphylaxis/anaphylactic shock.

Iodine allergy: (Z91.0)
Patients allergic to iodine are at an increased risk of adverse drug reactions when exposed to iodine-containing contrast media and patients who report previous allergic reactions to contrast agents should be carefully evaluated as to the need for the investigation. If the investigation is considered essential, the patient should be pre-treated with steroids and antihistamines before proceeding.

- Corticosteroids (intermediate-acting) e.g.:
- Prednisone, oral, 50 mg given 13 hours, 7 hours, and 1 hour before the procedure. *LoE:II*[iv]

Contrast-Induced Nephrotoxicity (CIN) is an important consideration; it may result in permanent renal impairment with significant effects on longevity. This is particularly important in an environment with limited access to renal replacement therapy. Before referring any patient for an

investigation involving contrast use, carefully weigh up the individuals' potential risk of CIN against potential benefits (the likelihood of detecting a condition for which a significant therapeutic intervention is available).

CIN is variously defined as either a 25% or a 50% rise on pre-contrast creatinine levels, or an absolute creatinine increase of more than 25 micromol/L. CIN is rare in individuals with normal renal function[v,vi] .

Factors that increase the risk of CIN include: diabetes, pre-existing renal impairment, age >75 years, anaemia, cardiac failure, hypotension and the volume of contrast media injected[vii,viii].

The probability of developing a 25% rise in creatinine after cardiac catheterisation in patients given 200 mL of non-ionic contrast media is linked to co-morbidity[vii]:

CIN risk	None	Anaemia	>75 yrs	CCF or low BP	>1 risk factor
No diabetes					
eGFR>60	7.5%	7.5%	7.5%	15%	15%
eGFR 40–60	7.5%	15%	15%	15%	15%
eGFR 20–40	7.5%	15%	15%	15%	25%
eGFR<20	15%	15%	25%	25%	25%
Diabetes					
eGFR>60	7.5%	15%	15%	15%	25%
eGFR 40–60	15%	15%	15%	25%	25%
eGFR 20–40	15%	25%	25%	25%	25%
eGFR<20	15%	25%	25%	25%	55%

The probability of needing dialysis after cardiac catheterisation is correlated with the risk of CIN[vii]:

CIN risk	7.5%	15%	25%	55%
Dialysis risk	0.04%	0.12%	1.1%	13%

Reducing the risk of developing CIN

There is no clear evidence that any specific medication is protective against the development of CIN. However, meticulous attention to fluid balance is important in patients at higher risk, as dehydration increases the risk of CIN.

Patients on metformin should be monitored for deterioration in renal function post procedure, as there is a small risk of precipitating lactic acidosis. In high risk patients it may be advisable to omit metformin for 48 hours after contrast injection while monitoring serum creatinine.

References:

[i] Wang CL, Cohan RH, Ellis JH, Caoili EM, Wang G, Francis IR. Frequency, outcome, and appropriateness of treatment of nonionic iodinated contrast media reactions. AJR2008; 191:409-415.http://www.ncbi.nlm.nih.gov/pubmed/18647910

[ii] Katayama H, Yamaguchi K, Kozuka T, Takashima T, Seez P, Matsuura K. Adverse reactions to ionic and nonionic contrast media. A report from the Japanese Committee on the Safety of Contrast Media. Radiology1990; 175:621-628. http://www.ncbi.nlm.nih.gov/pubmed/2343107

[iii] Caro JJ, Trindade E, McGregor M. The risks of death and of severe nonfatal reactions with high- vs low-osmolality contrast media: a meta-analysis. AJR1991;156:825-832. http://www.ncbi.nlm.nih.gov/pubmed/1825900

[iv] Prednisone, oral (iodine allergy): American College of Radiology. ACR Manual on Contrast Media, 2018, version 10.3. https://www.acr.org/Clinical-Resources/Contrast-Manual

Prednisone, oral: Tramèr MR, von Elm E, Loubeyre P, Hauser C. Pharmacological prevention of serious anaphylactic reactions due to iodinated contrast media: systematic review. BMJ. 2006 Sep 30;333(7570):675. https://www.ncbi.nlm.nih.gov/pubmed/16880193

Prednisone, oral: Lasser EC, Berry CC, Talner LB, Santini LC, Lang EK, Gerber FH, Stolberg HO. Pretreatment with corticosteroids to alleviate reactions to intravenous contrast material. N Engl J Med. 1987 Oct 1;317(14):845-9. https://www.ncbi.nlm.nih.gov/pubmed/3627208

[v] McDonald JS, McDonald RJ, Comin J, Williamson EE, Katzberg RW, Murad MH, Kallmes DF. Frequency of acute kidney injury following intravenous contrast medium administration: a systematic review and meta-analysis. Radiology. 2013 Apr;267(1):119-28.http://www.ncbi.nlm.nih.gov/pubmed/23319662

[vi] Davenport MS, Khalatbari S, Cohan RH, Dillman JR, Myles JD, Ellis JH. Contrast material-induced nephrotoxicity and intravenous low-osmolality iodinated contrast material: risk stratification by using estimated glomerular filtration rate. Radiology. 2013 Sep;268(3):719-28.http://www.ncbi.nlm.nih.gov/pubmed/23579046

[vii] McCullough PA, Adam A, Becker CR, Davidson C, Lameire N, Stacul F, Tumlin J; CIN Consensus Working Panel. Risk prediction of contrast-induced nephropathy.Am JCardiol. 2006 Sep 18;98(6A):27K-36K. http://www.ncbi.nlm.nih.gov/pubmed/16949378

[viii] Mehran R, Aymong ED, Nikolsky E, Lasic Z, Iakovou I, Fahy M, Mintz GS, Lansky AJ, Moses JW, Stone GW, Leon MB, Dangas G. A simple risk score for prediction of contrast-induced nephropathy after percutaneous coronary intervention: development and initial validation. J Am CollCardiol. 2004 Oct 6;44(7):1393-9.http://www.ncbi.nlm.nih.gov/pubmed/15464318

CHAPTER 23

ADULT CRITICAL CARE

23.1 INTRODUCTION AND PRINCIPLES OF CRITICAL CARE

INTRODUCTION

Critical care is the discipline that entails specialised medical and nursing care for patients who have, are at risk of, or are recovering from serious, life-threatening injuries and illnesses.

Critical care involves constant, intensive monitoring and comprehensive care including multiple modalities of vital physiologic organ support to sustain life during a period of life-threatening organ system insufficiency. Additionally, it involves intensive resuscitation and appropriate end-of-life care.

Critical care is usually delivered in the intensive care unit (ICU). However, it actually consists of a continuum of care provided throughout the health care chain including the pre-hospital environment, emergency department, hospital ward, high-care wards, and follow-up clinic.

LoE:IVb

Effective critical care requires, if possible, a multidisciplinary team to deal with these complex patients. In addition to medical and nursing personnel, such multidisciplinary teams must include inter alia physiotherapists, occupational therapists, dieticians, critical care technologists and social workers.

23.1.1 GENERAL PRINCIPLES OF PHARMACOLOGY IN CRITICAL ILLNESS

» Pharmacokinetic (PK, “what the body does to the drug”) and pharmacodynamic (PD, “what the drug does to the body”) variations in critical care patients occur secondary to underlying illness, rapidly changing multiorgan dysfunction, and the use of multiple supportive modalities.
» Therapeutic response and clinical outcomes are affected by altered drug absorption, plasma protein binding, volume of distribution, renal and hepatic clearance, and affinity of binding of drug molecules to target receptors. These PK and PD changes in critical illness can contribute to

suboptimal dosing, adverse outcomes, increased risk of medication errors, and adverse drug reactions.

» Loading doses may be required to achieve timeous therapeutic responses (e.g. phenytoin, beta-lactam, antimicrobials, vancomycin), especially for medicines with a long plasma half-life. Maintenance doses should be adjusted based on extent and trend of organ dysfunction, and clinical indication for the therapy.
» Careful dose titration based on clinical observation is required for medications with a rapid onset of action, or where vital parameters can be readily monitored.
» Therapeutic drug monitoring (TDM) is recommended, where possible, to assist in dose adjustment.
» Where renal replacement therapy is used, dosing should be tailored to account for changes in volume of distribution and clearance of medications.
» Polypharmacy may contribute to adverse outcomes secondary to drug interactions or toxicity.

LoE:IVb[ii]

23.2 RESPIRATORY SUPPORT

DESCRIPTION

The purpose of mechanical ventilation is to support the work of breathing, ensure adequate oxygenation, facilitate clearance of carbon dioxide, and minimise the trauma caused by ventilatory support.

Indications for mechanical ventilation include:

» Hypoxaemic respiratory failure
» Excessive work of breathing:
  – Inability to meet normal respiratory demands due to respiratory muscle weakness, e.g. Guillain-Barre Syndrome, opioid toxicity, or suxamethonium apnoea. Indicated by elevated PCO_2, or reduced minute ventilation via respiratory rate or tidal volume.
  – Inability to meet increased respiratory demand, e.g. asthma, chronic obstructive pulmonary disease (COPD), metabolic acidosis. Indicated by a PCO_2 that can be low, normal, or high but is often inappropriately high for clinical scenario; tachypnoea; respiratory distress; impending fatigue.
» Neuroprotection: patient with brain injury that requires mechanical ventilation for PCO_2 and PO_2 control.

GENERAL MEASURES

Concomitant respiratory support using strategies such as high flow nasal oxygenation, non-invasive mechanical ventilation, and invasive mechanical ventilation.

A detailed ventilation management strategy including initiation, titration and weaning of ventilation is presented in Appendix 23.I.

23.3 CARDIOVASCULAR SUPPORT

DESCRIPTION

Patients are often admitted to ICU for cardiovascular support, the commonest reason being for the treatment of shock. Although it is important to treat the underlying cause, patients may need cardiovascular monitoring and support in ICU while this is happening.

GENERAL MEASURES

In the critically ill patient, the following should be considered:

» Parenteral dosing of medications.
» Balanced salt solutions for resuscitation.

Monitoring should include (1) continuous ECG, oxygenation (SpO_2, arterial blood gases), (2) continuous blood pressure monitoring (preferably invasive blood pressure monitoring if available), (3) central venous pressure, and (4) urine output.

For cardiac arrest: see Section 20.1: Cardiac arrest in adults.
For post-cardiac arrest care: see Section 20.2: Post-cardiac arrest care.
For Acute Coronary Syndromes see Section 3.2.1: ST elevation myocardial infarction (STEMI) and Section 3.2.2: Non-ST elevation myocardial infarction (NSTEMI) and Unstable angina (UA).
For dysrhythmias: see Section 3.3: Cardiac dysrhythmias.
For hypertension: see Section 3.6: Hypertension.
For hypertensive urgency: see Section 3.6.2: Hypertensive urgency.
For hypertensive emergency: see Section 3.6.3: Hypertensive crisis, Hypertensive emergency.
For Acute cardiac failure see acute pulmonary oedema: Section 20.10: Pulmonary oedema, acute andCongestive Cardiac Failure: Section 3.4: Congestive cardiac failure (CCF).

23.3.1 SHOCK

R57

DESCRIPTION

Shock is defined as a state where perfusion is inadequate to meet the metabolic needs at a cellular level. There are various forms of shock each requiring their own specific treatment.

LoE:IVb[iii]

GENERAL MEASURES

The therapeutic aim for all types of shock is to restore perfusion and maintain an adequate blood pressure, e.g. Mean Arterial Pressure (MAP) >65 mmHg.

Management includes fluid therapy and administration of vasoactive medication that may vary depending on the type of shock (see Section 20.12: Shock):
For hypovolaemic shock: see Section 20.12.1: Hypovolaemic shock.
For distributive shock: see Section 20.12.2: Distributive shock.
For anaphylactic shock: see Section 20.7: Anaphylaxis/ anaphylactic shock.
For neurogenic shock: see Section 20.12.2.1: Neurogenic shock.
For septic shock: see Sections 20.12.2.2: Septic shock and Section 23.10: Sepsis in ICU.
For cardiogenic shock: see Section 20.12.3: Cardiogenic shock.
For obstructive shock: see Section 20.12.4: Obstructive shock.

MEDICINE TREATMENT

Fluid therapy

Balanced salt solutions are the preferred resuscitation fluids for shock.
Adequacy of fluid resuscitation should be guided by measures of fluid responsiveness.

LoE:IIIb[iv]

CAUTION
Avoid colloids for shock resuscitation in patients with sepsis and acute kidney injury.

LoE:IIIb[v]

Vasoactive therapy

Vasoactive therapy is indicated in a shocked patient that fails to respond to fluid therapy.

- Adrenaline (epinephrine), IV, 0.01 to 1.0 mcg/kg/min as a continuous infusion.
  - Aim to achieve a target MAP >65 mmHg within 30 minutes.

LoE:IVb[vi]

<u>If shock is suspected to be cardiogenic in origin:</u>

- Dobutamine, IV, 5 to 20 mcg/kg/min as a continuous infusion.

LoE:IVb[vii]

FLUID THERAPY FOR SHOCK

DESCRIPTION

» Balanced salt solutions are the preferred resuscitation fluids for shock.
» Adequacy of fluid resuscitation should be guided by measures of fluid responsiveness.

LoE:IIIb[viii]

CAUTION
Avoid colloids for shock resuscitation in patients with sepsis and acute kidney injury.

LoE:IIIb[ix]

VASOACTIVE MEDICINES FOR SHOCK

DESCRIPTION

Vasoactive therapy is indicated in a shocked patient that fails to respond to fluid therapy.

MEDICINE TREATMENT

- Adrenaline (epinephrine), IV, 0.01 to 1.0 mcg/kg/min as a continuous infusion.
  - Aim to achieve a target MAP >65 mmHg within 30 minutes.

LoE:IVb[x]

<u>If shock is suspected to be cardiogenic in origin:</u>

- Dobutamine, IV, 5 to 20 mcg/kg/min as a continuous infusion.

LoE:IVb[xi]

23.4 RENAL SUPPORT

DESCRIPTION

Acute kidney injury (AKI) in critical care is a complex, heterogenous clinical syndrome presenting with varying severities, trajectories, and outcomes.

LoE: IVb[xii]

See Section 7.1.4: Acute Kidney Injury, for further details.

Table 23.1: Staging/Severity of Acute Kidney Injury

Stage	Serum creatinine	Urine output
1	1.5 to 1.9 times baseline **OR** ≥26.5 µmol/l (≥0.3 mg/dl) increase	<0.5 ml/kg/h for 6 to 12 hours

2	2.0 to 2.9 times baseline	<0.5 ml/kg/h for ≥12 hours
3	3 times baseline **OR** Increase in serum creatinine to ≥353.6 µmol/l (≥4.0 mg/dl) **OR** Initiation of kidney replacement therapy **OR** In patients <18 years, decrease in eGFR to <35 ml/min per 1.73 m^2	<0.3 ml/kg/h for ≥24 hours **OR** Anuria for ≥12 hours

Taken from: Kidney Disease: Improving Global Outcomes (KDIGO). Acute Kidney Injury (AKI). 2012 Kidney Disease: Improving Global Outcomes (KDIGO) Clinical Practice Guideline for Acute Kidney Injury (AKI). 2012. Available at: https://kdigo.org/guidelines/acute-kidney-injury/

LoE:IVb[xiii]

GENERAL MEASURES

In all patients at risk for, and with AKI:

» Avoid nephrotoxic agents (e.g. aminoglycosides; amphotericin B, NSAIDs).
  – Where medication cannot be avoided, dose appropriately with use of therapeutic drug monitoring where available.
» Dose-adjust medications for reduced GFR.
» Ensure volume status is appropriate.
» Ensure optimal perfusion pressure.
» Consider functional haemodynamic monitoring.
» Monitor urine output (UO) and serum creatinine.
» Avoid hyperglycaemia.
» Consider alternatives to radiocontrast material.
» Search for reversible causes and treat.
» Consider invasive diagnostic workup.

Fluid therapy

» Use balanced salt solutions.
» For patients at high risk of AKI that also require imaging with iodine-based contrast media (e.g. eGFR <30 ml/min/1.73m^2, renal transplant, large volume of contrast medium to be used, intra-arterial administration of contrast medium), ensure adequate intravenous volume expansion with 0.9% sodium chloride solution if not already volume replete.

Nutrition in acute kidney injury

» Provide total energy intake of 20-30 kCal/kg/d in all AKI stages.
» Feeds may be given orally, enterally, or parenterally depending on gut functionality and integrity.

» Do not restrict protein intake with the goal of preventing or delaying Kidney Replacement Therapy (KRT).
» Consult a dietitian as necessary and refer to the National Department of Health Clinical Nutrition Guidelines.

LoE:IVb[xiv]

CAUTION

The following drugs are NOT RECOMMENDED for the prevention of AKI:
» Diuretics.
» Low dose dopamine.
» N-acetyl cysteine in critically ill patients with hypotension or for prevention in post-surgical AKI.

The following class of drug is NOT RECOMMENDED for the treatment of AKI:
» Diuretics (except in the management of fluid overload).

23.4.1 KIDNEY REPLACEMENT THERAPY (KRT)

DESCRIPTION

Acute kidney injury (AKI) may affect 60% of ICU patients with up to two-thirds of these patients going on to require kidney replacement therapy (KRT). *LoE:IVb*[xv]

KRT is commonly used in critically ill patients to achieve solute clearance, maintain acid-base status, and remove fluid excess.

Indications for acute Kidney Replacement Therapy (RRT):
» Stage 3 acute kidney injury deemed unlikely to resolve in the next few days.
» Refractory fluid overload.
» Clinical features of uraemia (e.g. gastritis, pericarditis, delirium, seizures).
» Life threatening acidosis.
» Refractory hyperkalaemia.
» Life threatening overdoses requiring KRT removal (e.g. lithium, theophylline, methanol, ethylene glycol, carbamazepine, and valproate).

Choice of mode of KRT:
» KRT may be continuous (CKRT) or intermittent (IKRT) and includes sustained low efficiency dialysis (SLED).
» There is no evidence that one method is superior compared to the others.
» CKRT is preferable in patients with hemodynamic instability, acute brain injury, increased intracranial pressure, generalized cerebral oedema, or liver failure.

MEDICINE TREATMENT

To reduce circuit hypercoagulability:

- Unfractionated Heparin, 5000 units diluted in 50ml 0.9% sodium chloride (100 units/ml), administered directly into the RRT circuit.
  - Initial bolus: 10 to 20 units/kg.
  - Continue running infusion at 5 to 10 units/kg/hour.
  - Monitor using daily Activated Partial Thromboplastin Time (aPTT).
  - Maintain aPTT between 45 to 55 seconds.

LoE:IVb[xvi]

OR

- Enoxaparin, SC, 40mg daily

LoE:IVb[xvii]

Note:

» Only use heparin if there is no bleeding risk. Use saline flushes if there is a significant risk of bleeding.

23.5 HAEMATOLOGICAL SUPPORT

23.5.1 THROMBOPROPHYLAXIS

DESCRIPTION

See Section 2.8: Venous thrombo-embolism.

GENERAL MEASURES

» All critically ill patients should receive pharmacological (i.e. unfractionated heparin, low-molecular-weight heparin [LMWH]) OR mechanical (intermittent pneumatic compression devices) thromboprophylaxis.

» Pharmacological thromboprophylaxis is superior to mechanical prophylaxis and should be used, unless contraindicated.

» If mechanical thromboprophylaxis is used, it should be provided with intermittent pneumatic compression devices which fit the patient well and cover both legs up to mid-thigh.

MEDICINE TREATMENT

- Low-molecular weight heparin (LMWH), e.g.
- Enoxaparin, SC, 40 mg daily.
  - Reduce dose to 20 mg daily if eGFR <30 ml/min.

LoE:IVb[xviii]

If LMWH is unavailable or contraindicated:

- Unfractionated heparin, SC, 5000 IU 12 hourly.

LoE:IVb[xix]

Note:
» Dose of enoxaparin must be adjusted in kidney disease and for patients with increased body mass.
» Avoid pharmacological thromboprophylaxis in patients with active bleeding, significant coagulopathy, or elevated risk for spontaneous or procedural bleeding.

23.5.2 ANAEMIA IN CRITICAL CARE
D64.9

DESCRIPTION
» Anaemia is common in critical illness.
» Anaemia results in reduced tissue oxygen delivery which may cause or worsen organ dysfunction. The underlying cause should be investigated and treated.
» Avoid unnecessary phlebotomy to reduce the risk of iatrogenic anaemia.
» The benefits of treating anaemia must always be weighed against the risks of blood transfusion.

GENERAL MEASURES
Transfusion triggers:
» The transfusion trigger is the haemoglobin (Hb) level at which one should consider a blood transfusion.
» The final decision to transfuse red blood cells should also consider the patient's clinical condition.
» Transfuse the patient to obtain an Hb above the transfusion trigger depending on the type of bleeding.

Non-bleeding patient:
In the non-bleeding patient, an Hb <7 g/dl is an appropriate transfusion trigger.

This includes patients with:
» Septic shock.
» Trauma without bleeding.
» Upper gastrointestinal bleeding.

Note:
» Elderly patients, and those with stable coronary artery disease do not appear to require a higher transfusion threshold.
» Uncertainty is noted for the following clinical scenarios:
  – critically ill patients with an acute coronary syndrome,
  – traumatic brain injury,
  – cerebrovascular accidents,
  – critically ill oncology patients.

» Transfusion may be appropriate in these scenarios in a patient with a Hb of 7 to 9 g/dl after considering the patient's clinical condition.

Bleeding patient:
The decision to transfuse the bleeding patient should not be based on a single Hb level, but should be determined by the:
» Amount and rapidity of blood loss.
» Likelihood of bleeding control.
» Physiological state of the patient.

Non-transfusion alternatives:
» Cell-salvage (blood salvage) may reduce the need for red blood cell transfusions, if available.

MEDICINE TREATMENT

- Red blood cells, IV, one unit immediately.
  - Only one unit of red blood cells should be ordered and transfused at a time. After each unit, the need for another unit should be reviewed prior to ordering the next unit.
  - Exceptions to this include large volume blood loss where a massive transfusion protocol may be more appropriate (see Section 23.5.7: Massive transfusion protocol).

LoE:IVb[xx]

CAUTION
» Intravenous iron should not be used as it does not appear to reduce transfusion requirements or improve outcomes in the critically ill patient.
» Erythropoietin should not be used in the critically ill patient unless indicated, as it has minimal effect on transfusion requirements, does not improve patient outcomes, and may be associated with adverse effects including thrombosis.

23.5.3 THROMBOCYTOPAENIA AND PLATELET DYSFUNCTION IN CRITICAL CARE

D69.6

DESCRIPTION

Qualitative and quantitative platelet disorders are common in critically ill patients and may be due to decreased production of platelets or increased consumption/sequestration.
Common causes of thrombocytopaenia and/or platelet dysfunction include sepsis, blood loss, dilutional thrombocytopaenia, medical conditions (e.g. uraemia), and medications including antiplatelet drugs (e.g. aspirin and clopidogrel) and heparin.

- Heparin-induced thrombocytopaenia should be considered in a patient whose platelet count decreases by >50% within 5 to 10 days of initiating heparin, especially if thrombotic complications have also developed. If this occurs, STOP all heparin products and consult a specialist.

The decision to transfuse platelets depends on:
» Whether the patient is bleeding.
» Whether the patient is to undergo a procedure.
» Aetiology of the thrombocytopaenia.
» Patient's platelet count.
» Results of coagulation testing.

LoE:IIIb[xxi]

Platelet transfusions are indicated in the following settings:
» Prophylactic: if platelet count <20 x 10^9/L.
  – A platelet count of <10 x 10^9/L is an acceptable alternative if the patient is not septic, not bleeding, and has a slow decline in platelet count.
» Prophylactic prior to invasive procedures/surgery:
  – Indicated if platelet count <50 x 10^9/L. Alternative thresholds may be used for the following indications:
    - Epidural catheter placement/removal: <75 x 10^9/L.
    - Neurosurgery or posterior ophthalmic surgery: <100 x 10^9/L.
    - Patients with intracranial haemorrhage: <100 x 10^9/L.
» Empiric: in large volume blood transfusion (where more than 4 units of packed cells required).
» Therapeutic: if platelet count <50 x 10^9/L and the patient is bleeding.
  – Transfusion may be deferred in the presence of normal thromboelastography (where available).

LoE:IVb[xxii]

GENERAL MEASURES

An assessment of haemostasis should be conducted with viscoelastic testing where available, e.g. thromboelastography (TEG), as this provides a functional assessment of whole blood clotting. A normal viscoelastic test may eliminate the need for a platelet transfusion even in the presence of thrombocytopaenia.

General measures to reduce bleeding in patients with thrombocytopaenia or platelet dysfunction include:
» Careful review of all anticoagulant and antiplatelet medication.
» Thorough assessment of other components of the coagulation system.
» Attention to maintaining normothermia and eucalcaemia.

Aspirin and clopidogrel are the most commonly used antiplatelet medications, and their antiplatelet effects may last up to 7 days. The need for platelet transfusions in the setting of platelet dysfunction should be discussed with a specialist.

MEDICINE TREATMENT

- Platelet cells, IV, one unit immediately.
  - One unit of pooled platelets should be transfused at a time.

Note:

» The need for further platelet transfusions should be based on platelet count, viscoelastic testing (if available), and the presence or absence of ongoing bleeding.

REFERRAL

» Heparin induced thrombocytopaenia: Consult a specialist.
» Platelet transfusions in the setting of platelet dysfunction: Consult a specialist.

23.5.4 PLASMA TRANSFUSION

DESCRIPTION

Plasma transfusions may be needed in the following scenarios:

» Coagulopathy due to multiple factor deficiencies, e.g. disseminated intravascular coagulation (DIC), or large volume blood loss.
» Thrombotic thrombocytopaenic purpura.
» Scoline apnoea.

Where available, viscoelastic testing (e.g. thromboelastography/TEG) should complement or replace standard coagulation testing as this provides a more clinically relevant assessment of functional coagulation.

Consult a specialist for further advice as necessary.

Choice of plasma product

Fresh frozen plasma (FFP) and lyophilized or freeze-dried plasma (FDP) may be treated as clinically interchangeable products with respect to their coagulant effect.

Indications for plasma transfusion

» Prophylaxis: prior to invasive procedures/surgery if International Normalised Ratio (INR) >2.
» Empiric: Large volume blood transfusion (>4 units of packed cells required. See Section 23.5.7: Massive transfusion protocol.).

» Therapeutic: if patient is bleeding and has an INR >2.

MEDICINE TREATMENT

Plasma Transfusion

For prophylaxis or therapy:

- Freeze-dried plasma, IV, 15 mL/kg immediately.
  - Repeat dose if the patient's clinical response and/or the coagulation function testing results indicate continued need.

Empiric use in large volume blood transfusion:

- Freeze-dried plasma, IV, 1 unit immediately.
  - Should be given for every unit of red blood cells when it is anticipated that >4 units of red blood cells will be required.

LoE:IVb[xxiii]

23.5.5 COAGULATION FACTORS

DESCRIPTION

Cryoprecipitate

» Cryoprecipitate is a source of fibrinogen, factor VIII, factor XIII, and von Willebrand factor.
» Active bleeding with a low fibrinogen level (<2 g/L) is the main indication for cryoprecipitate in critical care and is common in obstetric haemorrhage and trauma.
» Cryoprecipitate administration may also be guided by viscoelastic testing in major haemorrhage.

MEDICINE TREATMENT

- Cryoprecipitate, IV, 1 unit per 10 kg total body weight (South African National Blood Services), or 1 pooled unit (Western Cape Blood Services).

LoE:IVb[xxiv]

Vitamin K-dependent clotting factors:

For warfarin poisoning, see Section: 19.19 Anticoagulant (Warfarin and Rodenticide Superwarfarin) Poisoning.

For other coagulation factor-related disorders, see Chapter 2: Blood And Blood Forming Organs.

23.5.6 ANTIFIBRINOLYTIC MEDICATION

DESCRIPTION

Tranexamic acid is an antifibrinolytic agent that acts by inhibiting the activation of plasminogen, an enzyme responsible for fibrinolysis. Tranexamic acid may be considered in the following settings:

» Adjunctive medication in the prevention and treatment of bleeding.
» Where viscoelastic testing shows evidence of hyperfibrinolysis.

MEDICINE TREATMENT

Severe trauma (if given within 3 hours):

- Tranexamic acid, IV:
  - Loading dose: 1 g over 10 minutes as a bolus infusion.
  - Maintenance dose: 1 g added to 100 ml 0.9% saline over 8 hours as an infusion.

LoE:Ia[xxv]

Bleeding postpartum obstetric patients:

- Tranexamic acid, IV, 1 g over 10 minutes as a bolus infusion.

If bleeding persists (after 30 minutes):

- Tranexamic acid, IV, 1 g added to 100 mL 0.9% saline over 8 hours as an infusion.

LoE:Ia[xxvi]

Note:

» Benefit is greatest if initiated in the 1st hour. Initiation of tranexamic acid more than 3 hours after the initial insult may increase the risk of bleeding and mortality.

23.5.7 MASSIVE TRANSFUSION PROTOCOL

DESCRIPTION

Major haemorrhage may be defined as blood loss >150 ml/min, loss of >50% of blood volume in 3 hours, or loss of entire blood volume in 24 hours.

A massive transfusion may also be defined by the transfusion of >4 units of red blood cells in 1 hour, replacement of >50% of blood volume in 3 hours (>5 units in 3 hours), or the replacement of entire blood volume in 24 hours (>10 units in 24 hours).

LoE:IVb[xxvii]

In the setting of major haemorrhage, blood and blood products are most efficiently and effectively administered using a massive transfusion protocol (MTP).

Essentials of the protocol:

» The massive transfusion protocol is designed to facilitate the transfusion of large volumes of blood (at least 6 units of red blood cells) and blood products.

» MTP aims to avoid acute coagulopathy in major haemorrhage that is associated with trauma and other causes during the resuscitation phase.

» Blood components are given in fixed ratios initially. Further blood product administration is ideally guided by point of care coagulation testing.

» An MTP should be a collaboration between the treating unit/institution and the providing blood service. The exact details of the protocol will differ depending on the specifics of the treating unit/institution. (See Figure 23.1 below for an example of a massive transfusion protocol.)

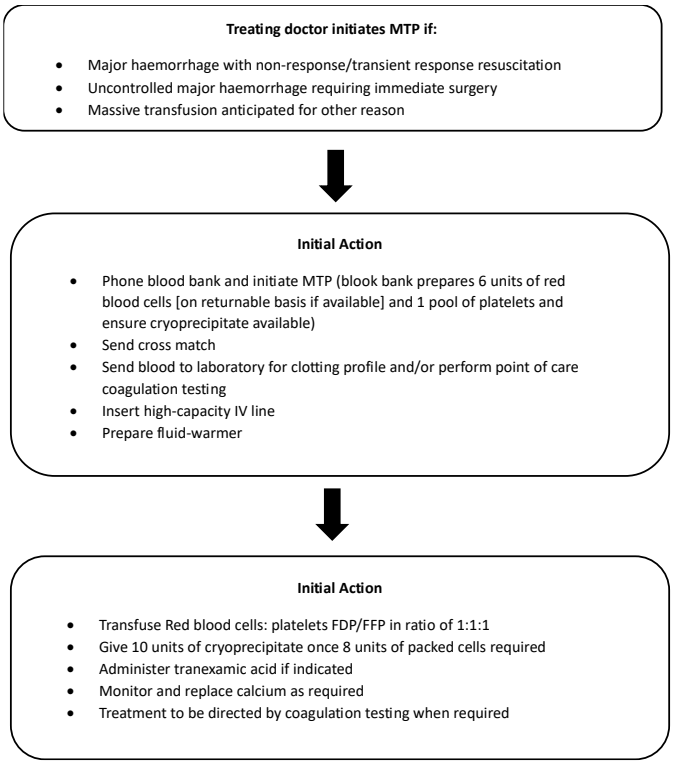


Figure 23.1 Massive Transfusion Protocol Approach

23.6 NEURO-PSYCHOLOGICAL SUPPORT

DESCRIPTION

ICU patients are treated with many interventions that may be distressing and uncomfortable. Pain, restlessness, agitation, and delirium may have untoward effects.

LoE:IVb[xxviii]

23.6.1 PAIN MANAGEMENT

R52

DESCRIPTION

Prioritization of effective pain control is imperative for optimising the care of critically ill patients. Recognizing the impact of uncontrolled pain on anxiety and psychological distress also underscores the importance of a holistic approach to care. A comprehensive treatment approach for critically ill patients places a strong emphasis on timely and appropriate pain management, positively influences physiological stability and patient, reduces the incidence of complications, and improves overall quality of care. Current guidelines recommend that pain management should be guided by routine pain assessment. An example of a pain assessment tool is given in Table 23.1.

LoE:Ivb[xxix]

Table 23.1 Behavioural Pain Scale

Item	Description	Score
Facial Expression	Relaxed	1
	Partially tightened e.g., brow lowering	2
	Fully tightened e.g. eyelid closing	3
	Grimacing	4
Upper limb movements	No movement	1
	Partially Bent	2
	Fully bent with finger flexion	3
	Permanently retracted	4
Compliance with mechanical ventilation	Tolerating movement	1
	Coughing but tolerating ventilation for most of the time	2
	Fighting ventilator	3
	Unable to control ventilation	4
BPS score ranges from 3 (no pain) to 12 (maximum pain)		

Taken From: Sessler CN, Gosnell MS, Grap MJ, Brophy GM, O'Neal PV, Keane KA, et al. The Richmond Agitation-Sedation Scale: validity and reliability in adult intensive care unit patients. Am J Respir Crit Care Med. 2002 Nov 15;166(10):1338–44.

LoE:Ivb[xxx]

GENERAL MEASURES

» Pharmacological treatment includes opioid and non-opioid medicines.
» Pain should be treated before sedation is considered.
» Table 23.2 provides some important characteristics to be considered when prescribing commonly used analgesics in the ICU.
» Paracetamol and ketamine are recommended adjuncts to reduce opioid consumption.
» Non-pharmacological strategies such as positioning, music, massage and relaxation therapies may also be beneficial.
» See Section 12.4: Perioperative analgesia for more details on pain management.

MEDICINE TREATMENT

Parenteral therapy

<u>If paracetamol is required and patient is nil per mouth:</u>

- Paracetamol, IV, 1 g 6 hourly for 24 hours. (Specialist initiated.)
  - If required beyond 24 hours prescription would need to be authorised by a specialist.

LoE:Ivb[xxxi]

Regional anaesthesia

» Local anaesthetic agents can be considered for regional analgesia e.g. epidural (see Section 12.8: Anaesthesia, epidural), para-vertebral, and peripheral nerve blocks where expertise is available and appropriate (see Section 12.9: Peripheral nerve block or wound infiltration).

Table 23.2: Commonly used analgesics in the ICU

Drug	Category of Analgesic	Loading dose	Maintenance dose	Onset	Duration	Adverse effects
Paracetamol (PO/IV)	Simple analgesic	-	PO: 1 g/6h IV: 1 g/6h	PO: 30 mins IV: 5 mins	4 to 6 h	Hepatotoxic. Interacts with warfarin (↑INR) and CYP 450 inducers.
Tramadol (PO/IV) *Less potent (20% of morphine)*	Weak opioid	-	PO/IV: 50 to 100 mg/6h	PO: 30 mins IV: 15 mins	3 to 6 h	Less constipation and respiratory depression.
Fentanyl (IV)	Strong opioid	20 to 100 mcg	50 to 100 mcg/h	1 min	0.5 to 1 h	Nausea, constipation. Respiratory depression. Muscle rigidity.
Morphine (IV)		2 to 10 mg	2 to 5 mg/h	5 min	4 h	Nausea, constipation
Ketamine (IV)	Adjunctive analgesic	0.25 to 0.5 mg/kg	0.05 to 0.4 mg/kg/h *Very low dose (1-2 mcg/kg/h- opioid sparing)* Higher doses may be required in polytrauma and Traumatic Brain Injury.	30 sec	10 mins	Sympathetic stimulation. Hallucinations, delirium. Increased secretion. Dissociative state. Liver/renal dysfunction → active metabolite accumulation.

Guidance for prescribing: Combinations of medicines from different classes may be considered where needed. *LoE:Ivb*[xxxii]

23.6.2 SEDATION

DESCRIPTION

Most patients may not require routine sedation, however, patients with the following conditions may require pharmacological sedation:

» severe acute respiratory failure,
» status epilepticus,
» raised intracranial pressure/ traumatic brain injury,
» status asthmaticus.

GENERAL MEASURES

For patients whom sedation is indicated, a combination with analgesia (analgo-sedation) is recommended. This means that the pain is treated first, with consideration made for sedation where required.

Its use is guided by a sedation assessment tool, e.g. Richmond Agitation Sedation Scale (RASS; see Table 23.3). The target RASS score is -2 to 0, with lighter sedation preferred over deeper sedation. It is important to exclude and manage delirium before routine sedation is administered (see Section 23.6.3: Delirium in critical care, below).

LoE:Ivb[xxxiii]

Table 23.3: Richmond agitation sedation scale (RASS)

Score	Term	Description	Type of stimulation
+4	Combative	Overly combative, violent, immediate danger to staff	Without Stimulation
+3	Very agitated	Pulls or removes tube(s) or catheter(s); aggressive	
+2	Agitated	Frequent non-purposeful movement, fights ventilator	
+1	Restless	Anxious but movements not aggressive or vigorous	
0	Alert and calm		
-1	Drowsy	Not fully alert, but has sustained awakening (eye opening/ eye contact) to *voice* (≥10 seconds)	Verbal Stimulation
-2	Light sedation	Briefly awakens with eye contact to *voice* (<10 seconds)	
-3	Moderate sedation	Movement or eye opening to *voice* (but no eye contact)	
-4	Deep sedation	No response to voice, but movement or eye opening to *physical stimulation*	Physical Stimulation
-5	Unarousable	No response to *voice or physical stimulation*	

Taken From: Khan BA, Perkins AJ, Gao S, Hui SL, Campbell NL, Farber MO, et al. The CAM-ICU-7 Delirium Severity Scale: A Novel Delirium Severity Instrument for Use in the Intensive Care Unit. Crit Care Med. 2017 May;45(5):851–7.

LoE:IVb[xxxiv]

The properties of the different sedative agents can be used to help select an appropriate choice. See Table 23.4 for commonly used sedative agents and their properties in critically ill patients. The choice of agent being dictated by patient clinical presentation and any contraindications.

Table 23.4: Commonly used sedatives in the ICU

Drug	Load	Maintenance	Onset	Duration	Adverse effects
Propofol IV	-	5 to 50 mcg/kg/min or 50-200 mg/h Titrate every 5min	1 min	3 to 10 mins	PRIS — Vasodilation, inotropy ↑Triglyceride
Midazolam IV	1 to 5 mg	1 to 5 mg/h	<5 mins	30 mins	↑delirium risk
Lorazepam IV	1 to 4 mg	1 to 5 mg/h	15 mins	6 to 8 h	↑delirium risk

PRIS = Propofol related infusion syndrome

LoE:IVb[xxxv]

23.6.3 DELIRIUM IN CRITICAL CARE

F05

DESCRIPTION

The risk of delirium is increased in patients with severe illness, with a prevalence of 40-60% in non-ventilated patients, and 50-80% in mechanically ventilated patients. Diagnosing delirium can be difficult due to its highly variable presentation. Symptoms may fluctuate over the course of a day with periods of reduced attention, awareness, and other features of cognitive dysfunction, along with periods of lucidity. Patients may present with agitated, disruptive and/or uncooperative behaviour (hyperactivity), sluggishness, lethargy, stupor (hypoactivity), or a mixture of these features. This variability is further complicated by the influence of analgo-sedatives and medical and surgical interventions. Delirium is associated with increased duration of mechanical ventilation, length of ICU and hospital stay, long-term cognitive impairment, and mortality.

Risk factors for delirium include: advanced age; pre-existing dementia; history of coma and/or other neurological disorders, hearing and visual impairment, pre-ICU emergency surgery or trauma, blood transfusions; and increased severity of underlying illness. Precipitating factors include sleep deprivation, pain, environmental insults (e.g., noise, physical restraint use, catheters), and psychoactive medicine use (e.g., benzodiazepines).

LoE:IIb[xxxvi]

GENERAL MEASURES

Prevention, early recognition, and non-pharmacological management steps are recommended while the underlying critical illness is treated.

Strategies to prevent delirium include:

- regular patient reorientation
- noise reduction
- cognitive stimulation
- visual and hearing aids
- minimize use of sedative medicines
- early mobilization
- adequate hydration

» Recognise delirium early with daily clinical assessment and screening using a validated tool (see CAM-ICU 7 screening tool in Table 23.5).
» Be alert to hypoactive delirium, where the patient may be poorly responsive to questions.
» Screen for delirium in the absence of sedative effects.
» Use screening to explain what the symptoms mean and to reassure the patient and their relatives.

» Exclude:
  - Alcohol withdrawal delirium.
  - Psychosis, mania, or depression (either new onset or related to discontinuation of chronic medicines).

General management includes:
» Searching for, and correction of, precipitating factors.
» Intensified preventative strategies, particularly:
  - Pain control.
  - Minimising sedation.
  - Maintaining a calm, containing environment.
  - Re-orientating and explain all procedures to the patient.
  - Educating visitors (encourage visits).
  - Maintaining normal circadian rhythm.

Table 23.5: CAM-ICU 7 screening tool

Items	Grading
1. Acute Onset or Fluctuation of Mental Status Has the patient's mental status changed from his/her baseline? **OR** Has the patient had any fluctuation in mental status in the past 24 hours as evidenced by fluctuation on a sedation/ level of consciousness scale (i.e., RASS/SAS, GCS), or previous delirium assessment?	Absent = 0 Present = 1
2. Inattention Say to the patient "*I am going to read you a series of 10 letters. Whenever you hear the letter "A," indicate by squeezing my hand." Read letters from the following letter list in a normal tone 3 seconds apart. <u>SAVEAHAART</u> (Errors are counted when the patient fails to squeeze on the letter "A" and when the patient squeezes on any letter other than "A")*	≥ 8 correct (absent): Give score of 0 4-7 correct (Present): Give score of 1 0-3 correct (Severe): Give score of 2
3. Altered Level of Consciousness Present if the actual RASS score is anything other than alert and calm (zero)	RASS = 0 (Absent) Give score of 0 RASS = 1 or -1 (Present) Give score of 1 RASS >1 or RASS <-1 (Severely altered) Give score of 2
4. Disorganized Thinking <u>Yes/No Questions</u> i. Will a stone float on water? ii. Are there fish in the sea? iii. Does one pound weigh more than two pounds? iv. Can you use a hammer to pound a nail? Errors are counted when the patient incorrectly answers a question. <u>Command:</u> Say to patient "Hold up this many fingers (Hold two fingers in front of patient). Then say, "Now do the same with the other hand." (Do not repeat number of fingers.) An error is counted if patient is unable to complete the entire command.	Correct ≥ 4 (Absent) Give score of 0 Correct = 2-3 (Present) Give score of 1 Correct ≤ 1 (Severely disorganised) Give score of 2
Interpretation: 0-2: no delirium, 3-5: mild to moderate delirium, and 6-7: severe delirium.	

CAM-ICU: Confusion Assessment Method for the Intensive Care Unit; Richmond Agitation Sedation Scale; SAS: Sedation- Agitation Scale; GCS: Glasgow Coma Scale

Khan BA, Perkins AJ, Gao S, Hui SL, Campbell NL, Farber MO, Chlan LL, Boustani MA. The Confusion Assessment Method for the ICU-7 Delirium Severity Scale: A Novel Delirium Severity Instrument for Use in the ICU. Crit Care Med. 2017 May;45(5):851-857. doi: 10.1097/CCM.0000000000002368. PMID: 28263192; PMCID: PMC5392153.

LoE:IVb[xxxvii]

MEDICINE TREATMENT

For treatment recommendations, see Section 20.8: Delirium with perceptual disturbances.

For delirium with severe agitation and/or aggression: see Section: 15.1 Aggressive disruptive behaviour in adults.

Note:

» Antipsychotic medicines may reduce agitated behaviour and distress, but there is no evidence that they treat the delirium itself.
» For alcohol withdrawal see Section 15.8.1.1: Alcohol Withdrawal Delirium (Delirium Tremens).

23.6.4 MOOD DISORDERS

See Section 15.3: Mood disorders.

23.6.5 SEIZURES

See Section 14.4: Epileptic seizures.

23.6.6 INTRACRANIAL PRESSURE MANAGEMENT

See Section 14.14.2: Brain oedema due to traumatic injury.

23.7 GASTRO-INTESTINAL SUPPORT

23.7.1 NUTRITION

DESCRIPTION

Critically ill patients have increased nutritional requirements due to an increased metabolic rate. Therefore, they require careful management of their nutritional requirements.

GENERAL MEASURES

» Commence nutritional support as soon as possible.
» Oral, enteral or parenteral route should be initiated once it is safe to reduce the risk of adverse events associated with the overuse of enteral/parenteral feeding.
» Consider choice of feed to meet patient-specific fluid, caloric, and protein requirements.

REFERRAL

» Consult dietitian as appropriate and refer to the National Department of Health Clinical Nutrition Guidelines (https://criticalpoint.co.za/wp-content/uploads/2016/10/DOH-enteral-nutrition-guidelines.pdf and

https://criticalpoint.co.za/wp-content/uploads/2017/09/DOHParenteral-nutrition-guidelines.pdf).

See Section 12.13.1: Nutritional support. LoE:IVb[xxxviii]

23.7.2 STRESS ULCER PROPHYLAXIS

K25.0/K25.1/K25.2/K25.3/K25.9/K26.0/K26.1/K26.2/K26.3/K26.9/K27.0/K27.1/K27.2/K27.3/K27.9

DESCRIPTION

Stress-related mucosal disease is an acute, erosive gastritis comprising conditions that range from stress-related injury to stress ulcers. Stress-related injury is due to superficial mucosal damage that manifests as erosions, while stress ulcers are due to deep, focal mucosal damage penetrating the submucosa. Stress ulcers occur in up to 9% of all patients admitted to critical care units, and the risk is higher in those that do not receive stress ulcer prophylaxis. Stress ulcers can cause clinically important gastrointestinal bleeding and lead to hemodynamic instability, an increased need for red blood cell transfusions, increased length of stay in the ICU, as well as increased mortality.

LoE:IVb[xxxix]

GENERAL MEASURES

» Initiate oral or enteral feeding as soon as it is safe to do so.

MEDICINE TRATMENT

- Pantoprazole, IV, 40 mg daily.
  - Stop stress ulcer prophylaxis once the patient is tolerating enteral feeds as prolonged PPI use increases the risk of hospital acquired pneumonia.

LoE:IIb[xl]

23.7.3 REGURGITATION AND ASPIRATION

K21.0/K21.9/J69.0

DESCRIPTION

Gastroesophageal reflux is common in patients treated in critical care units. Contributing factors include mechanical ventilation causing elevated intrathoracic pressure, reduced/absent lower oesophageal sphincter tone, and GI dysmotility. Gastroesophageal reflux is an important risk factor for aspiration, pneumonia, and acute lung injury.

GENERAL MEASURES

» Avoid regurgitation of gastric contents by decreasing intragastric pressure.
» Nurse patient at 30-45 degrees with the head up.
» Obtain Chest X-ray to confirm suspected aspiration.
» Use a nasogastric tube and confirm placement with x-ray imaging and/or pH analysis of aspirate.
» Maintain oropharyngeal hygiene. *LoE:IVb[xli]*
» If aspiration suspected, suction oropharynx and endotracheal tube thoroughly.

23.7.4 DIARRHOEA

A09.0/K52.8/K52.9

DESCRIPTION

Up to 62% of critically ill patients experience at least one episode of diarrhoea during their admission. Risk factors include the use of enteral nutrition (particularly those with high osmolarity), duration of antimicrobial use, and the use of suppositories. Diarrhoea increases the risk of complications including renal dysfunction, dehydration, electrolyte disturbance, as well as impairment of dermal integrity. There is also evidence that the development of GI problems is associated with worse outcome in critically ill patients.

LoE:IVb[xlii]

GENERAL MEASURES

» Send stool specimens to evaluate potential causes.

Consider *Clostridium (Clostridioides) difficile* diarrhoea

» (See Section 1.3.4: *Clostridium difficile* diarrhoea) and feed-related diarrhoea as potential causes.

MEDICINE TREATMENT

» Treatment will depend on the identified aetiology.
» See Section 1.3: Diarrhoea for specific treatment.

23.7.5 LIVER SUPPORT

See Section 1.2.2: Liver Failure, Acute.

REFERRAL

Consult specialist unit to evaluate suitability for liver transplantation.

23.7.6. ACUTE SEVERE PANCREATITIS

K85.0/K85.1/K85.2/K85.3/K85.8/K85.9

DESCRIPTION

Approximately 10–30% of patients with acute pancreatitis develop a severe form that requires management in a critical care unit. Acute severe pancreatitis is a life-threatening disease with an in-hospital mortality rate of up to 15%. The severity of acute pancreatitis is determined by the development of organ failure for >48 hours and local complications including infected (peri-) pancreatic necrosis, haemorrhagic or systemic complications, and infective pancreatitis.

LoE:IVb[xliii]

GENERAL MEASURES

For general management of acute pancreatitis, see Section 1.1.6: Pancreatitis, Acute.

Measures specific to critical care management

» Provide supportive therapy for organ failure, including fluid support (see Section 23.3.1: Fluid therapy for shock).
» Address the underlying cause e.g. gall stones.
» Treat sepsis (see Section 23.10: Sepsis in ICU).

REFERRAL

Refer for surgical consultation for complications including:

» Pancreatic abscess.
» Pancreatic necrosis.
» Pancreatic pseudocyst.
» Abdominal compartment syndrome.

23.7.7 ACUTE CHOLECYSTITIS

K81.0

DESCRIPTION

Acute acalculous cholecystitis is a specific complication of critical illness that warrants organ support, antimicrobial therapy, and consultation for surgical intervention.

LoE:IVb[xliv]

GENERAL MEASURES

See Section 1.2.7: Cholecystitis, acute and cholangitis, acute.

REFERRAL

All patients for surgical consultation and intervention.

23.7.8 ABDOMINAL COMPARTMENT SYNDROME

R19.8

DESCRIPTION

Abdominal compartment syndrome is defined as the presence of intra-abdominal hypertension, with sustained intra-abdominal pressures exceeding 20 mmHg, along with evidence of new-onset organ dysfunction. Abdominal compartment syndrome can be classified as primary, i.e. due to direct injury of the abdomen or pelvic region, or secondary, i.e. referred pressure from other compartments. Mechanisms of causes resulting in abdominal compartment syndrome can be broadly categorised into decreased abdominal wall compliance, increased intraluminal contents, collection of contents in the abdominal cavity, and capillary leak and fluid resuscitation. Abdominal compartment syndrome is associated with severe critical illness and multi-organ failure and has a high risk of mortality (40-100%) which necessitates urgent intervention.

LoE:IVb[xiv]

GENERAL MEASURES

Relieve intra-abdominal pressure via:

- nasogastric tube
- urinary catheter
- drainage of intra-abdominal collections
- appropriate positioning
- sedation
- analgesia
- muscle relaxation (if ventilated)
- surgical decompression

REFERRAL

» Consider surgical consultation for decompression.

23.8 METABOLIC AND ENDOCRINE SUPPORT

23.8.1 THYROID DISORDERS IN CRITICALLY ILL PATIENTS

DESCRIPTION

Non-specific alterations can occur in critically ill patients. The majority revert to normality upon full recovery from the underlying physical insult. The transient dysfunction is attributed to changes in thyroid stimulating hormone (TSH) regulation, altered peripheral metabolism of thyroid hormones, and altered binding of thyroid hormone to thyroid binding globulin.

CAUTION
Thyroid function assessment is not routinely recommended and should be guided by the clinical history and evaluation.

23.8.1.1 SICK EUTHYROID SYNDROME
E07.8

DESCRIPTION
Thyroid dysfunction occurs as a response to the oxidative stress of critical illness and is proportional to the severity of disease. Low T3 levels are often seen soon after ICU admission. High T4 may also be noted early but subsides over time with multiple organ dysfunction syndrome. Thyroid function frequently returns to normal within a few months of disease resolution.

23.8.1.2 HYPERTHYROIDISM
See Section 8.18: Hyperthyroidism.

23.8.1.3 THYROID CRISIS
E05.5

DESCRIPTION
See Section 8.18.5: Thyroid Crisis.

GENERAL MEASURES
» Treat precipitant factors.

Hemodynamic:
» For volume resuscitation: use balanced salt solutions.

Respiratory
» Supplemental oxygen
» Ventilatory support

Hyperthermia
» Incorporate cooling/ targeted temperature management.
» Use cool, balanced salt solutions initially.
» Apply ice packs and cooling blankets.
» Dextrose solutions may be suitable for continued cooling to cope with high metabolic demands.
» Treat cardiac arrhythmias, if necessary (see Section 3.3. Cardiac dysrhythmias).

Metabolic:
» Monitor and correct electrolyte abnormalities.

MEDICINE TREATMENT
For details, see Section 8.18.5: Thyroid crisis.

Beta-adrenergic receptor blockade:
- Atenolol, oral, 50 mg daily.
  - Increase to 100 mg if response is suboptimal and patient can tolerate increased beta-adrenergic receptor blockade.
  - An NG tube may be used for administration if an IV formulation is unavailable.

LoE:IVb[xlvi]

Hyperthermia:
- Paracetamol, oral, 1 g, 4 to 6 hourly as required (to a maximum of 4 g in 24 hours).
  - Maximum single dose: 15 mg/kg/dose.

23.8.1.4 HYPOTHYROIDISM
See Section 8.11: Hypothyroidism.

23.8.1.5 MYXOEDEMA COMA
E03.5/E03.9

DESCRIPTION
Myxoedema coma is an uncommon condition characterized by severe hypothyroidism which may present with an altered mental status, lethargy, hypothermia, decreased organ function, and other non-specific features associated with hypothyroidism. Myxoedema coma is a life-threatening condition with a high mortality rate of up to 30%; rapid recognition is critical to avoid end-organ damage. Despite the name, coma is an uncommon presentation and is not necessary to make the diagnosis, however, its presence is a poor prognostic indicator.

LoE:IVb[xlvii]

GENERAL MEASURES
» Treat precipitant factor.
» Provide organ support, as needed.
» Use passive rewarming measures.
» Manage hypoglycaemia and hyponatraemia.
» Be cautious of upper airway compromise due to macroglossia and/or supraglottic myxoedema.

LoE:IVb[xlviii]

MEDICINE TREATMENT

- Hydrocortisone, IV, 100 mg 8 hourly.

Thyroid hormone replacement

- Levothyroxine (T4), oral.
  - Loading dose: 200 mcg as a single dose.
  - Maintenance dose: 100 mcg, daily.
  - Medication can be administered via NG tube if an IV formulation is unavailable.

LoE:IVb[xlix]

23.8.2 ADRENAL INSUFFICIENCY

See Section 8.2: Adrenal insufficiency (Addison Disease).

23.8.2.1 RELATIVE ADRENAL INSUFFICIENCY

E27.4/E27.9

DESCRIPTION

This is a transient, disproportionate reduction of glucocorticoids in relation to the severity of stress. Note that absolute cortisol levels may be normal. The prevalence of relative adrenal insufficiency is high in septic shock. See Section 23.10: Sepsis in ICU for more details.

MEDICINE TREATMENT

See Section 23.10: Sepsis in ICU.

23.8.2.2 ADDISONIAN CRISIS

E27.2

DESCRIPTION

Acute adrenal (Addisonian) crisis is a potentially fatal condition that occurs because of insufficient circulating corticosteroids. It is usually caused by impairment of the hypothalamic-pituitary axis but may also be due to anatomic destruction of the adrenal gland (e.g. in disseminated tuberculosis or fungal infections, or other disease that infiltrate the adrenal gland), adrenal haemorrhage (e.g. septicaemia induced Waterhouse-Friderichsen syndrome), or more commonly, steroid withdrawal.

GENERAL MEASURES

Acute adrenal insufficiency is an emergency and requires immediate therapy.

Principles of management include:

» Treating precipitating cause.

» Providing organ support.

MEDICINE TREATMENT

- Hydrocortisone, IV, 100 mg 6 hourly.

LoE:IVb[i]

23.8.3 HYPOGLYCAEMIA

E10.0/E10.6/E11.0/E11.6/E12.0/E12.0/E12.6/E13.0/E13.6/E14.0/E14.6/E16.0/E16.1/E16.2

DESCRIPTION

Hypoglycaemia, defined as a glucose concentration <4 mmol/L, is common in critically ill patients, and is associated with increased mortality. Risk factors associated with hypoglycaemia in critically ill patients include severity of illness, intensive/strict glucose control, continuous veno-venous haemodialysis, decreased nutritional feeds without adjustment of insulin infusions, prior diagnosis of diabetes mellitus, sepsis, and the need for inotropic support. See Section 8.6.1: Hypoglycaemia for further details.

GENERAL MEASURES

» Assess and treat precipitating factors.
» Maintain a target glucose concentration of 6 to 10 mmol/L.
» Monitor glucose every 15 minutes.
» Provide organ support (respiratory, cardiovascular, neurological).

LoE:IVb[ii]

MEDICINE TREATMENT

<u>If awake and alert:</u>

- Glucose, oral, 20 g, immediately.
  - Alternatively, a carbohydrate-rich supplement may be given if tolerated.

<u>If obtunded, or glucose level <2.5 mmol/L:</u>

- Dextrose 50%, IV, 20 ml immediately.

<u>If hypoglycaemia recurs or dextrose 50% IV solution is not available:</u>

- Glucagon, SC, 1 mg immediately.

LoE:IVb[iii]

23.8.4 HYPERGLYCAEMIA

E10.0-1/E11.0-1/E12.0-1/E13.0-1/E14.0-1/R73.9

DESCRIPTION

Hyperglycaemia (blood glucose concentration >11 mmol/L) occurs in up to 50% of critically ill patients (also called stress hyperglycaemia or critical illness hyperglycaemia). An elevated blood glucose in patients with previously

undiagnosed diabetes and without significantly elevated glycated haemoglobin (Hb_{A1c}) levels (>6.5%) is suggestive of stress hyperglycaemia.

LoE:IVb[iii]

Hyperglycaemia is associated with increased mortality, length of hospitalisation, and potentially an increased risk of hospital acquired infections.

See Section 8.6.2: Diabetic Ketoacidosis (DKA) And Hyperosmolar Hyperglycaemic State (HHS) for further details.

GENERAL MEASURES

» Maintain a glucose target in ICU: 6-10 mmol/L.
» Balanced salt solutions are preferred to normal saline for fluid resuscitation.
» Continuous insulin infusion therapy should be considered to achieve glycaemic targets.
» Risk of hypoglycaemia should be considered when choosing the method of insulin administration.

23.9 TOXICOLOGY IN ICU

DESCRIPTION

See Chapter 19: Poisonings.

GENERAL MEASURES

» Poisoning should always be considered in patients who present with an altered level of consciousness.
» A thorough collateral history and toxicology screen may assist with making the diagnosis.
» Toxicology screens; where available, may have varied diagnostic reliability in patients with suspected poisoning. These results should always be interpreted in conjunction with a comprehensive clinical assessment.
» Consider whether positive results are due to iatrogenic administration of sedatives/analgesics commonly used to manage patients.
» Exert due caution in making the diagnosis of brain death or deciding on neurological futility if poisoning have not been excluded. (See Section 23.12: End of life care, determination of death).
» Although patients may fit a specific toxidrome or have a history of ingesting a specific toxin, consider whether patients may have ingested more than one toxin.

For guidance on specific toxins, see Chapter 19: Poisonings.

23.10 SEPSIS IN ICU

A41.9

DEFINITION

Sepsis is defined as life-threatening organ dysfunction caused by a dysregulated host response to infection. Organ dysfunction is defined as an acute increase in SOFA (Sequential Organ Failure Assessment) score of at least 2 points. Patients with sepsis have a significantly higher mortality than those with an infection without sepsis.

LoE:IVb[liv]

Septic shock is characterised by hypotension requiring vasopressors to maintain MAP ≥65 mmHg despite adequate fluid resuscitation, plus a serum lactate >2 mmol/l. Patients with septic shock have a significantly higher mortality (>20%) than those with sepsis without septic shock.

Table 23.6: Sequential organ failure assessment (SOFA) score

System	Score				
	0	1	2	3	4
Respiration					
PaO_2/FIO_2 mmHg (kPa)	≥400 (53.3)	<400 (53.3)	<300 (40)	<200 (26.7)	<100 (13.3)
				with respiratory support	
Coagulation					
Platelets, $x10^3$ µ/L	≥ 150	<150	<100	<50	<20
Liver					
Bilirubin in µmol/L (mg/dL)	<1.2 (20)	1.2-1.9 (20-32)	2.0-5.9 (33-101)	6.0-11.9 (102-204)	>12.0 (204)
Cardiovascular	MAP ≥ 70mmHg	MAP < 70mmHg	Dopamine <5[a] or dobutamine (any dose)[a]	Dopamine 5.1.-15[a] or adrenaline ≤ 0.1[a]	Dopamine >15[a] or adrenaline >0.1[a]
Central Nervous System					
Glasgow Coma Scale[b]	15	13-14	10-11	6-9	<6
Serum creatinine in µmol/L (mg/dl)	110 (<1.2)	110-170 (1.2-1.9)	171-299 (2.0-3.4)	300-440 (3.5-4.9)	440 (>5.0)
Urine output, ml per day				<500	<200

FIO_2 = Fraction of inspired oxygen; MAP = mean arterial pressure; PaO2 = partial pressure of oxygen

[a] Catecholamine doses are given as per $\mu g.kg^{-1}.min^{-1}$ for at least 1 h.

[b] Glasgow Coma Scale scores range from 3 to 15; higher score indicates less severe neurological disorder

Adapted from: Vincent JL, Moreno R, Takala J, et al. The SOFA (Sepsis-related Organ Failure Assessment) score to describe organ dysfunction/failure. Intensive Care Med. 1996;22:707–710 *LoE:IVb*[iv]

23.10.1 SEPSIS IN ICU: INITIAL RESUSCITATION

MEDICINE TREATMENT

- Balanced-salt solution crystalloid, IV, 30 ml/kg over 3 hours.
  - Aim for an initial haemodynamic target of MAP >65 mmHg.
  - Further fluid challenge should be guided by one or more of the following:
    - Dynamic markers of fluid responsiveness, e.g. passive leg raising, pulse pressure variation, stroke volume variation.
    - Lactate clearance: aim for a lactate clearance of >20% over 2 hours.
    - Capillary refill time: aim for a capillary refill time of <3 seconds. *LoE:IVb*[iv]

CAUTION
Avoid colloids for shock resuscitation in patients with sepsis and acute kidney injury.

23.10.2 SEPSIS IN ICU: HAEMODYNAMIC SUPPORT

MEDICINE TREATMENT

<u>If fluid therapy alone does not rapidly correct MAP to ≥65mmHg:</u>

- Adrenaline (epinephrine), IV, 0.01 to 1.0 mcg/kg/min given as an infusion.

LoE:IVb[vii]

  - Aim to achieve a target MAP >65 mmHg within 30 minutes.
  - Increasing the adrenaline infusion rate above 1 mcg/kg/min is not recommended in the absence of clear, reversible causes such as hypovolaemia, bleeding, tension pneumothorax etc.

<u>In patients with significant left ventricular dysfunction and no improvement with adrenaline,</u> **ADD:**

- Dobutamine, IV, 500 mg in 200 ml 0.9% saline as a continuous infusion.

- Start infusion at 5 ml/hr.
- Check MAP regularly (every 10 to 30 minutes until target is reached) and titrate infusion rate by 2.5 ml/hr to reach target MAP (≥65 mmHg).
- Infusion rates exceeding 20 ml/hr are usually not required.

Note: *LoE:IVb[lviii]*

» While noradrenaline is recommended in international guidelines as a first-line vasopressor for septic shock, there is no evidence that it offers additional benefits over adrenaline.
» Given the lack of availability and increased cost of noradrenaline, its routine use is not recommended.
» Dopamine should not be used due to an increased risk of mortality and arrhythmias.

LoE:IVb[lix]

23.10.3 SEPSIS IN ICU: ANTIMICROBIAL THERAPY

DESCRIPTION

Early administration of antimicrobial therapy is one of the most effective interventions to reduce mortality in patients with sepsis and should be treated as an emergency. Various aspects including timing of antimicrobials, choice of antimicrobial agent, and dosing require careful consideration.

Timing

» Start empirical antimicrobials therapy within 1 hour of the presumptive diagnosis of sepsis or septic shock.
» Take appropriate samples for microbiology, ideally prior to commencing or changing antimicrobials. However, do not delay antimicrobial administration to collect samples as the risk of mortality increases hourly in untreated sepsis.

Dosing

» See Appendix 1: Antimicrobial Medicines for antimicrobial-specific guidance on dosing.
» Prescribe the higher dose of an antimicrobial dosing range, provided there that it is safe to do so.
» Consider extending the duration of infusion for certain antimicrobials (notably beta-lactams, see note on continuous infusions below).
» The initial or loading dose does not need to be adjusted in the presence of renal dysfunction. However, subsequent dosing may require dose adjustment depending on renal function and the use of renal replacement therapy.

» Extending the infusion duration of beta-lactam antimicrobials may improve effectiveness by increasing the time above the MIC (See Table 23.7).

Table 23.7. Examples of possible continuous infusion dosing regimens

Antimicrobial	Loading dose	Maintenance dose
Amoxicillin/clavulanic acid A	1.2 g over 30 mins.	1.2 g infusion given over 4 hours, 6 hourly dosing interval. LoE:IIIb[lx]
Piperacillin/tazobactam W	4.5 g over 30 mins.	4.5 g infusion given over 4 hours, 6 hourly dosing interval.
Meropenem W	1 g over 30 mins.	1 g infusion given over 4 hours, 6 hourly dosing interval. LoE:IIIb[lxi]

Choice of antimicrobial

The causative organism is usually not known at the time of clinical deterioration. In view of this critically il patients should receive a broader spectrum agent while awaiting culture results followed by subsequent de-escalation to an agent with the narrowest spectrum that will treat the causative organism.

Choose appropriate broad-spectrum empiric antimicrobial therapy based on the following factors:

» Site of sepsis.
» Likely causative organisms.
» Risk factors for healthcare-associated infections: Hospitalisation for >48 hours, previous antimicrobial therapy or hospitalisation within 3 months, residence in long-term care facility, or chronic wound care.
» Local antibiograms.
» Patient factors: organ dysfunction, allergies.

When culture and sensitivity results are available and the clinical picture allows, change empiric antimicrobial therapy to the agent that has the narrowest spectrum and that is the most cost-effective. De-escalation is crucial in reducing selective pressure and combatting antimicrobial resistance.

Additional antimicrobials that are prescribed empirically to treat suspected atypical and anaerobic organisms, MRSA, or invasive fungal infections should be carefully considered based on current local epidemiology, and deferred until microbiology results are available if possible. Discuss with a clinical microbiologist. Source control is essential in managing infections in all patients, including those in ICU. Effective source control should be achieved as soon as possible.

Table 23.8: Example of an ICU Empiric Antimicrobial Guideline

Infection	Community Acquired Infection	Healthcare Associated Infection	Suspected Multidrug resistance
Upper Gastro-intestinal tract (GIT)	Amoxicillin/clavulanic acid (A) ± Gentamycin# (A) + Fluconazole	Piperacillin-tazobactam (W) ± Amikacin# (W) + Fluconazole	Meropenem* (W) + Fluconazole
Lower GIT Urological Gynaecological	Amoxicillin/clavulanic acid (A) ± Gentamycin# (A)	Piperacillin-tazobactam (W) ± Amikacin# (W)	Meropenem* (W)
	For pelvic inflammatory disease, add: Metronidazole (A)		
Infected pancreatic necrosis (suspected)		Piperacillin-tazobactam (W) ± amikacin (A)	Meropenem (W)
Pneumonia in HIV-negative patient	Amoxicillin/clavulanic acid (A) + Azithromycin (W)	Piperacillin-tazobactam (W) ± Amikacin# (W) ± Vancomycin^ (W)	Meropenem* (W) ± Vancomycin^ (W)
Pneumonia in HIV-positive patient (with bilateral infiltrates)	+Cotrimoxazole (A) + Anti-TB Rx*		
Meningitis	Ceftriaxone (W)	Meropenem (W)	
Skin and soft tissue	Amoxicillin/clavulanic acid (A)	Piperacillin-tazobactam (W) ± Vancomycin^ (W)	Meropenem* (W) ± Vancomycin^ (W)
	For necrotizing fasciitis, add: Clindamycin (A) ± Gentamycin# (A)	+ Clindamycin (W) + Amikacin# (W)	+ Clindamycin (W)

Infection	Community Acquired Infection	Healthcare Associated Infection	Suspected Multidrug resistance
Catheter-related bloodstream infection		Piperacillin-tazobactam (W) ± Amikacin# (W) ± Vancomycin^ (W)	Meropenem (W) ± Vancomycin^ (W)
Infective endocarditis	Ampicillin (A) + Cloxacillin (A) + Gentamicin (A)	Meropenem (W) ± Vancomycin^ (W)	
Tetanus	Metronidazole (A)		
Suspected Clostridium Difficile Enterocolitis	Enteral Vancomycin (W) (IV prep via NGT)		

^ If from unit with high rate of MRSA (methicillin resistant staphylococcus aureus) or recent MRSA within ICU.
# Decision to embark on dual therapy with an aminoglycoside should be based on assessment of potential benefits of expanded antibiotic coverage based on local susceptibility patterns.

Note:

» Recommendations included in the table may require modifications subject to local resistance patterns.
» The choice of carbapenem depends on unit policy/most cost-effective option. If the patient has seizures/ CNS disorder, consider meropenem over imipenem.
» For patients with AKI (acute kidney injury): If serious gram-negative sepsis suspected, consider continuing aminoglycoside with therapeutic drug monitoring, or prescribe beta-lactam antimicrobial as monotherapy, depending on clinical scenario.

Carbapenem-resistant Enterobacterales bacteraemia

U83.7

Carbapenem-resistant Enterobacterales (CRE) are Gram-negative bacteria with reduced susceptibility to at least one of the carbapenem antimicrobials. The clinical outcomes of patients infected with CREs are worse than for other infections and it is imperative that these organisms do not spread to other patients in the unit. Strict adherence to infection control is essential.

These patients should be discussed with clinical microbiologists and infectious disease physicians. Choose an antimicrobial agent that tests susceptible and is active at the site of the infection. Often, limited therapeutic options are available.

In these cases, ceftazidime-avibactam can be considered for CRE bacteraemia, in consultation with a specialist and antimicrobials stewardship team, where the infecting organism is proven to be sensitive to ceftazidime-avibactam on bacterial culture. Use should be avoided in patients with a poor prognosis. Duration of treatment is dependent on indication and clinical response. Duration of treatment should not exceed 14 days.

MEDICINE TREATMENT

- Ceftazidime-avibactam, 2.5 g, IV, 8 hourly. W (Microbiologist or Infectious Disease specialist initiated).

Use should be avoided in patients with a poor prognosis.

- Duration of treatment is dependent on indication for treatment and clinical response.
- Duration of treatment should not exceed 14 days.

LoE:IVb[lxii]

If the patient is suspected to have a fungal infection, start empirical therapy:

- Amphotericin B, IV, 1 mg/kg/day for 2 weeks or until diagnostic results confirm/exclude fungal infection.

  OR

  - Fluconazole, IV:
    - Loading dose: 800 mg daily.
    - Maintenance dose: 400 mg daily.

LoE:IIa[lxiii]

Note:

The choice between these antifungals should be determined by:

» presence of kidney disease and other organ dysfunction.
» previous anti-fungal therapy.
» local fungal sensitivity patterns.
» site of infection.

Duration of antimicrobial therapy

» Shorter durations of antimicrobial therapy may be effective. Please monitor clinical response closely.
» Duration of antimicrobial therapy may be individualised by the use of clinical response and biomarkers.
» Antimicrobials may be stopped 48 hours after clinical response or if procalcitonin levels drop below 0.5 ng/l or 80% of peak.
» The failure to respond to a short course of antimicrobials should prompt consideration of antimicrobial resistance or inadequate source control.
» Certain infections (infective endocarditis, empyema, septic arthritis, invasive fungal infections) may, however, still require prolonged antimicrobial therapy.

Source control
The specific anatomical site of infection should be identified as soon as possible and if source control is required (e.g. by surgical intervention) this should be done as soon as medically and logistically possible. Patients with sepsis and septic shock should undergo a period of stabilisation and optimisation prior to source control. This should have clearly defined targets, interventions, and timelines.

23.10.4 SEPSIS IN ICU: ADJUNCTIVE THERAPY

MEDICINE TREATMENT

Steroid Therapy
If the patient with shock requires ≥0.25 mcg/kg/min of adrenaline (epinephrine) for >4 hours:

- Hydrocortisone 50mg, IV, 6 hourly until resolution of shock.

LoE:IVb[lxiv]

Glycaemic control

» Blood glucose should be maintained between 6 to 10 mmol/l, using insulin therapy if required. See Sections 23.8.3: Hypoglycaemia and 23.8.4: Hyperglycaemia for further details.

23.11 SAFETY IN ICU

23.11.1 PATIENT SAFETY

Important patient safety issues in critical care include:

» Proper patient identification.
» Timely response to critical tests.
» Appropriate and safe use of clinical alarms.
» Improvement of staff communication.
» Appropriate and safe use of medicines.
» Infection prevention and control.

All patient safety incidents (PSI) are to be reported on the South African National Patient Safety Incident Reporting and Learning (NPSIRL) System and acted upon appropriately as per the processes of the system. (https://www.knowledgehub.org.za/elibrary/national-guideline-patient-safety-incident-reporting-and-learning-health-sector-south)

23.11.2 PATIENT TRANSFER AND HANDOVER

The following aspects need to be ensured before transferring critically ill patients:

» Decision to transfer is made by the responsible senior.
» Adequate and appropriate communication between referring and receiving teams.
» Experienced and well-trained transfer team capable of managing any deterioration.
» Patient to be stabilized as far as possible with on-going organ support provided for duration of transfer.
» Appropriately secured airway for transfer.
» Appropriate monitoring with sufficient battery back-up.
» Appropriate level of sedation and pain control.
» Adequate oxygen for transfer duration.
» Adequate volumes of medications and fluids for duration of transfer.
» Prevention of pressure damage and adequate wounds and fractures management.
» Emergency medications and equipment.
» Appropriate and detailed documentation to accompany patient.

Consider the following strategies to improve ICU handovers:
» Standardize the process into specific phases, for example:
  – Pre-handover preparation.
  – Equipment and technology handover.
  – Information handover.
  – Discussion and plan.
» Complete urgent clinical tasks before the information transfer.
» Allow only patient-specific discussions during verbal handovers.
» Require that all relevant team members be present.
» Provide training in team skills and communication.

23.12 END OF LIFE CARE

DESCRIPTION

When it has been assessed that continued therapy is unlikely to be beneficial, an active end-of-life (EOL) care process needs to be initiated. The following should be considered:
» In South Africa (SA), EOL care issues are regulated by *inter alia* The SA Constitution Act 108 of 1996, the Health Professional Act of 1974, the National Health Act 61 of 2003, HPCSA Ethical Guidelines (Booklets), Children's Act 38 of 2005 and Common Law.
» Health Care Workers (HCWs) are not obligated to provide treatments that they deem to be unnecessary, unethical, unreasonable, or non-beneficial, and as such may be withheld or withdrawn.
» The patient's wishes in the form of an advance directive (e.g. Living Will) must be taken into consideration with EOL decision-making.

» Build consensus among the multidisciplinary HCW team, patients, and/or their surrogate decisions makers, in a structured manner, by using clear communication skills.
» Timely and regular family conferences are essential to provide information (diagnosis, prognosis, therapy), address the family's concerns, gain insight into the patient's wishes, and understand family dynamics and coping mechanisms. (See Appendix 23.II for Family Meeting Form.)
» In South Africa, the legal surrogate decision maker is determined in the following order: (i) spouse/partner; (ii) parent; (iii) grandparent; (iv) major child; and (v) sibling.
» To resolve a disagreement, a second opinion from an independent practitioner, or a peer review team, or an ethics committee may be consulted. Legal recourse should be a last resort.
» The agreed management plan for EOL care, and decisions about the use of life-sustaining treatment within that plan, should be clearly documented in the patient's medical records.
» The method employed varies widely and is influenced by ICU protocols, physician beliefs, the clinical scenario as well as patient and family preferences. Additionally cultural factors, religious background (of the physician and the family) as well as the regional legal framework also influence the approach that is utilized.
» The patient may experience pain, anxiety, delirium, respiratory distress, dyspnoea, vomiting, excessive broncho-pulmonary secretions and stridor. It is the physician's medical and ethical responsibility to ensure these issues are prevented and appropriately managed.
» The HCW team may experience distress, anxiety and grief. A formal debriefing meeting should be held to alleviate HCW burnout by providing adequate emotional support in an atmosphere that is conducive of trust and mutual understanding.

LoE IVb: [lxv]

See Chapter 24: Medicines for palliative care for further details.

Definitions

» *Advanced Directive:* A legally-binding, pre-existing, pre-written document wherein the patient reflects their EOL care wishes during times of incapacitation that clinicians are expected to respect.
» *Withholding therapy*: Decision not to initiate or escalate a life-sustaining therapy or other therapies.
» *Withdrawing therapy*: Decision to actively stop current life-sustaining therapy.
» *Do Not Resuscitate (DNR) or No Cardiopulmonary Resuscitation (No CPR) orders*: Pre-emptive order to withhold cardiopulmonary resuscitation.

Determination of death

Brain death

Death is defined as the clinical endpoint characterized by the irreversible loss of consciousness and the inability to breathe. An accurate clinical examination is important to ensure the correct determination of death and should be performed in the absence of potential confounders (factors leading to an incorrect determination of death, e.g. poisoning, severe electrolyte derangements). If confounders are present, the clinical assessment should be deferred until these have resolved, or confirmatory testing is available to make a diagnosis of death.

A diagnosis of death requires the presence of 3 conditions: persistent coma, absence of brainstem reflexes, and the lack of ability to breathe independently/apnoea.

Table 23.9 presents a summary of the clinical assessment process. Full details can be accessed here: South African guidelines on the determination of death, http://www.samj.org.za/index.php/samj/article/view/13264/9746.

LoE IVb: [lxvi]

Table 23.9: Determination of brain death

Clinical domain	Test	Remarks
Coma	Apply pressure to the following areas: – condyles at the temporomandibular joint, – supra-orbital notches, – all four extremities.	– Non-spinal reflex responses are incompatible with a brain death diagnosis. – Consultation with an experienced practitioner is recommended if the origin of a response is unclear. – Ancillary testing may be needed if responses are ambiguous.
Brain-stem reflexes	– Pupillary light reflex. – Corneal reflex. – Pain response in trigeminal distribution. – Vestibulo-ocular reflex (Cold caloric test).	– All brain-stem reflexes must be absent to determine brain death. – Beware of drugs causing pupillary constriction or dilation, e.g. opioids or anticholinergic drugs. – Be mindful of spinal cord injuries – assess brainstem mediated response rather than peripheral sensation/motor function.
Apnoea test	– Pre-oxygenate the patient with 100% oxygen for 10 minutes. – Perform a baseline arterial blood gas. measurement. – Disconnect the patient from the mechanical ventilator. – Supply continuous oxygen via a T-piece (preferred) or through a catheter inserted through the endotracheal tube and placed above the carina. – Observe continuously for any spontaneous breathing.	– Only proceed with the apnoea test if all above reflexes are absent. – Apnoea must persist in the presence of an adequate stimulus to spontaneous ventilation, i.e. an arterial PaCO2 >60 mmHg (8 kPa) and an arterial pH <7.30. – Take an arterial blood gas to document the rise in PaCO2 and change in pH. At the end of the test, reconnect the patient to the mechanical ventilator. – Monitor the patient's SpO_2 throughout the procedure. – Testing should be aborted if spontaneous respirations, hypotension, hypoxaemia (SpO_2 <85%), or arrhythmia is noted.

Adapted from Thomson D, Joubert I, De Vasconcellos K, Paruk F, Mokogong S, Mathivha R, McCulloch M, Morrow B, Baker D, Rossouw B, Mdladla N, Richards GA, Welkovics N, Levy B, Coetzee I, Spruyt M, Ahmed N, Gopalan D. South African guidelines on the determination of death. South Afr J Crit Care. 2021 Mar 1;37(1):10.7196/SAJCC.2021v37i1b.466. doi: 10.7196/SAJCC.2021v37i1b.466. PMID: 37214191; PMCID: PMC10193841.

LoE IVb: [lxvii]

General remarks:

» The following features are incompatible with brain death: decerebrate or decorticate posturing, true extensor or flexor motor responses to painful stimuli or witnessed seizures.

Ancillary testing:
» When performed correctly, the clinical exam is the most accurate way of testing neurological function. Ancillary tests require the assumption of an intact neurological stimulus-integration-response arc.
» It is recommended that the clinical exam be completed to the fullest extent possible prior to conducting ancillary tests such as cerebral angiography, transcranial dopplers, radionuclide/scintigraphy studies, etc (see full details in the South African guidelines on the determination of death, http://www.samj.org.za/index.php/samj/article/view/13264/9746).

Circulatory death
Circulatory death is the preferred term when death is determined on circulatory grounds. This terminology is preferred to terms such as cardiac or cardiorespiratory death and is in alignment with the latest guidelines.

To make an assessment of death on circulatory grounds, one of the following criteria must be met:
» It is inappropriate to attempt cardiopulmonary resuscitation.
» Attempts at cardiopulmonary resuscitation have failed.
» Treatment aimed at sustaining life has been withdrawn. This may occur if further treatment is deemed unlikely to offer additional benefit to the patient, or to respect the patient's wishes via advanced directive, or as expressed by their legal surrogate decision maker.

The absence of mechanical cardiac function should be confirmed using a combination of the following:
» absence of a central pulse on palpation
» absence of heart sounds on auscultation.

In the hospital setting, circulatory cardiac function can also be assessed by looking for pulsatile flow with direct intra-arterial pressure monitoring, or by looking for contractile activity using echocardiography.

Once this has been determined, the patient should be observed by the person responsible for confirming circulatory death for at least five minutes for confirmation.

Note:
» Any spontaneous return of circulatory or respiratory activity during the five-minute observation period should prompt a reset and repeat of the observation period.
» Return of circulatory or respiratory activity is not an indication to begin resuscitation efforts where this has been determined to be inappropriate.

APPENDICES

APPENDIX 23.I: MANAGEMENT OF VENTILATION

1. Initiation of ventilation

Once a patient has been intubated and is appropriately sedated, the ventilator is set as follows:

a. Select the level of support:
   i. Assist-Control: Pressure Control or Volume Control
      The ventilator delivers the same breath during every inspiration, whether initiated by the ventilator or by the patient.
   ii. Synchronised Intermittent Ventilation: Pressure Control or Volume Control.
      Minimum rate is set, and patient may initiate additional supported breaths.
   iii. Spontaneous: Invasive Continuous Positive Airway Pressure (CPAP) with Pressure Support.
      All breaths are initiated by the patient (no set rate) and a pressure support above Positive End Expiratory Pressure (PEEP) is provided.
b. Select the level of supplemental oxygen concentration:
   i. F_iO_2 at 1 (or 100%).
c. Set the trigger:
   i. Machine Triggered: Respiratory Rate at 12 to 15 breaths per minute.
   ii. Patient Triggered: Sensitivity - Pressure 2cmH2O or Flow 1-2 L/min.
d. Set the Control:
   i. For Volume Control: set tidal volume at 5 to 8 ml/kg predicted body weight.
   ii. For Pressure Control: set the pressure above PEEP to 15 cmH2O (driving pressure).
e. Set the Cycle:
   i. Inspiratory: Expiratory Ratio at 1:2.
   ii. Flow Cycling: 30% of Maximum Inspiratory Flow.
f. Set the Baseline Pressure:
   i. Positive End Expiratory Pressure: 5cmH_2O.

The following should be monitored for the patient receiving invasive mechanical ventilation:

» Arterial blood gas.
» Pulse oximetry.
» All ventilator parameters.

2. Titration of Ventilation

a. Ventilation must constantly be titrated to the patient's changing needs.
b. Incrementally reduce FiO2 by 0.1 (10%) every 10 minutes to 0.4 (40%) keeping oxygen saturation (SpO_2) ≥95%.
   Patients with, or at risk of Acute respiratory distress syndrome (ARDS) are able to tolerate SpO_2 ≥88%.
c. Adjust settings to target PCO_2 of 4.5 to 6.0 kPa:
   i. A lower PCO_2 will be targeted to temporarily compensate for a metabolic acidosis while the cause is being corrected.
   ii. A PCO_2 of 4.2 to 4.8kPa may be targeted in brain injured patients.
   iii. A higher PCO_2 may be tolerated in patients with, or at risk of, ARDS to minimise the need for harmful ventilator settings (permissive hypercapnia).
   iv. Do not let respiratory acidosis develop such that pH <7.20.

Note:

» The above are targets are guidelines and sometimes cannot be met. In these instances, more injurious/aggressive settings may be required for short periods.
» Mechanical ventilation may also be provided non-invasively (NIV) via face mask (specific instructions to be obtained from consultant regarding patient selection and initial settings).

3. Weaning of Ventilation:

» Weaning of ventilation is a continuous process and cannot be separated from titration of ventilation described above: it is simply the reducing limb of ventilation titration.
» Once a patient is stable on mechanical ventilation and requirements are no longer increasing, ongoing attempts must be made at the progressive stepwise reduction of ventilatory support.
» Reduce ventilatory support, beginning in this order:
   a. FiO_2: aim for FiO_2 of 0.4 (40%).
   b. Respiratory Rate (RR):
      i. Make multiple attempts to reduce the RR for short periods till the patient starts taking spontaneous breaths.
      ii. If the spontaneous rate is >10/min, place the patient on Pressure support/ Continuous positive airway pressure (PS/CPAP).
      iii. Adjust pressure support to maintain tidal volume as needed.
      iv. Observe to see if stable:
         – Pressure Support: progressively reduce PS while maintaining tidal volume >6ml/kg and pH >7.3 until PS = 6 cmH_2O.

- PEEP: Reduce PEEP by 2cmH_2O till PEEP = 6 cmH_2O.

Note: the minimum levels of PS and PEEP able to be set may vary as per the make of the ventilator

» The patient is ready for liberation from the ventilator once the patient requires minimal ventilatory support as described above and is stable with:
  - SpO_2 >92%, RR between 10 and 30 breaths/min, tidal volume >6 ml/kg, and pH >7.3.
  - HR and BP within 20% of patient's normal; Minimal inotropic support; No new arrhythmias.
  - No respiratory distress: Alar flaring, Use of accessory muscles, Paradoxical abdominal movement.
  - No sweating.

» To assess patient readiness for extubation:
  - Assess for adequate level of consciousness, bulbar function, and muscle strength.
  - If patient can cough and maintain own airway, then consider extubation.
  - T-piece tests are no longer routinely recommended.

APPENDIX 23.II: FAMILY MEETING FORM

Date…… Time……. Chairperson……..……

Patient……...

Hospital Number……..……

Meeting Number ….	Name/s and details
Family members	
Nursing Staff	
Other persons	
Purpose	
Surrogate decision maker	
Other	

Points Discussed	Tick if yes	Comment
Current status		
Prognosis		
Patient's wishes		
Clinical advice		
Family opinion		
Nursing input		
Decision(s)agreed		
Special requests		
Do Not Resuscitate DNR status		
Other		

Name	Position (please tick)	Signature
	ICU Specialist	
	Nursing Sister	
	Surgeon/Clinician	
	Fellow	
	Registrar	
	Medical officer	
	Other-specify	

Signatures:

…….. ……

Doctor **Patient/Family Member**

……..

Witness

References:

[i] Principles of Critical Care: Marshall JC, Bosco L, Adhikari NK, Connolly B, Diaz JV, Dorman T, et al. What is an intensive care unit? A report of the task force of the World Federation of Societies of Intensive and Critical Care Medicine. J Crit Care. 2017 Feb;37:270-276. doi: 10.1016/j.jcrc.2016.07.015.

[ii] Principles of Critical Care: Chen J. Pharmacology in Critical Illness. In: Oropello JM, Pastores SM, Kvetan V. eds. Critical Care. McGraw Hill; Accessed April 04,2022.
https://accessmedicine.mhmedical.com/content.aspx?bookid=1944&sectionid=143516493)

[iii] Shock (Definition): Cecconi M, De Backer D, Antonelli M, Beale R, Bakker J, Hofer C, Jaeschke R, Mebazaa A, Pinsky MR, Teboul JL, Vincent JL, Rhodes A. Consensus on circulatory shock and hemodynamic monitoring. Task force of the European Society of Intensive Care Medicine. Intensive Care Med. 2014 Dec;40(12):1795-815. doi: 10.1007/s00134-014-3525-z. Epub 2014 Nov 13. PMID: 25392034; PMCID: PMC4239778.

[iv] Balanced salt solutions: NDoH, Affordable Medicines, EDP-Adult Hospital level. Medicine Review: Ringer Lactate for resuscitation in adults, updated review, August 2019. http://www.health.gov.za/
Li B, Zhao H, Zhang J, Yan Q, Li T, Liu L. Resuscitation Fluids in Septic Shock: A Network Meta Analysis of Randomized Controlled Trials. Shock. 2020 Jun;53(6):679-685. Doi:10.1097/SHK.0000000000001468. PMID: 31693630.
Rochwerg B, Alhazzani W, Sindi A, Heels-Ansdell D, Thabane L, Fox-Robichaud A, Mbuagbaw L, Szczeklik W, Alshamsi F, Altayyar S, Ip WC, Li G, Wang M, Wludarczyk A, Zhou Q, Guyatt GH, Cook DJ, Jaeschke R, Annane D; Fluids in Sepsis and Septic Shock Group. Fluid resuscitation in sepsis: a systematic review and network meta-analysis. Ann Intern Med. 2014 Sep 2;161(5):347-55. doi: 10.7326/M14-0178. PMID: 25047428..

[v] Fluid Therapy: Finfer S, Bellomo R, Boyce N, French J, Myburgh J, Norton R; SAFE Study Investigators. A comparison of albumin and saline for fluid resuscitation in the intensive care unit. N Engl J Med. 2004 May 27;350(22):2247-56. doi: 10.1056/NEJMoa040232. PMID: 15163774.
Crystalloid versus Hydroxyethyl Starch Trial (CHEST) Management Committee. The Crystalloid versus Hydroxyethyl Starch Trial: protocol for a multi-centre randomised controlled trial of fluid resuscitation with 6% hydroxyethyl starch (130/0.4) compared to 0.9% sodium chloride (saline) in intensive care patients on mortality. Intensive Care Med. 2011 May;37(5):816-23. doi: 10.1007/s00134-010-2117-9. Epub 2011 Feb 10. PMID: 21308360.

[vi] Vasopressors: National Department of Health: Affordable Medicines, EDP-Adult Hospital level. Medicine Review: Vasopressors, inotropes as monotherapy or in combination, April 2023. http://www.health.gov.za/. https://accessmedicine.mhmedical.com/content.aspx?bookid=1944&sectionid=143516493)
Evans L, Rhodes A, Alhazzani W, Antonelli M, Coopersmith CM, French C, Machado FR, Mcintyre L, Ostermann M, Prescott HC, Schorr C, Simpson S, Wiersinga WJ, Alshamsi F, Angus DC, Arabi Y, Azevedo L, Beale R, Beilman G, Belley-Cote E, Burry L, Cecconi M, Centofanti J, Coz Yataco A, De Waele J, Dellinger RP, Doi K, Du B, Estenssoro E, Ferrer R, Gomersall C, Hodgson C, Hylander Møller M, Iwashyna T, Jacob S, Kleinpell R, Klompas M, Koh Y, Kumar A, Kwizera A, Lobo S, Masur H, McGloughlin S, Mehta S, Mehta Y, Mer M, Nunnally M, Oczkowski S, Osborn T, Papathanassoglou E, Perner A, Puskarich M, Roberts J, Schweickert W, Seckel M, Sevransky J, Sprung CL, Welte T, Zimmerman J, Levy M. Surviving Sepsis Campaign: International Guidelines for Management of Sepsis and Septic Shock 2021. Crit Care Med. 2021 Nov 1;49(11):e1063-e1143. doi: 10.1097/CCM.0000000000005337. PMID: 34605781.

[vii] Dobuatamine, IV: South African Medicines Formulary. 14th Edition. Division of Clinical Pharmacology. University of Cape Town. 2022.
Dobutamine: MCC registered South African package insert: Pharmaplan Cardiject® powder for IV infusion, 250 mg/vial.
National Department of Health: National Department of Health: Essential Drugs Programme. Adult Hospital level STGs and EML. Chapter 20: Emergencies and Injuries.

[viii] Balanced salt solutions: NDoH, Affordable Medicines, EDP-Adult Hospital level. Medicine Review: Ringer Lactate for resuscitation in adults, updated review, August 2019. http://www.health.gov.za/
Li B, Zhao H, Zhang J, Yan Q, Li T, Liu L. Resuscitation Fluids in Septic Shock: A Network Meta-Analysis of Randomized Controlled Trials. Shock. 2020 Jun;53(6):679-685. Doi:10.1097/SHK.0000000000001468. PMID: 31693630.
Rochwerg B, Alhazzani W, Sindi A, Heels-Ansdell D, Thabane L, Fox-Robichaud A, Mbuagbaw L, Szczeklik W, Alshamsi F, Altayyar S, Ip WC, Li G, Wang M, Wludarczyk A, Zhou Q, Guyatt GH, Cook DJ, Jaeschke R, Annane D; Fluids in Sepsis and Septic Shock Group. Fluid resuscitation in sepsis: a systematic review and network meta-analysis. Ann Intern Med. 2014 Sep 2;161(5):347-55. doi: 10.7326/M14-0178. PMID: 25047428.

[ix] Finfer S, Bellomo R, Boyce N, French J, Myburgh J, Norton R; SAFE Study Investigators. A comparison of albumin and saline for fluid resuscitation in the intensive care unit. N Engl J Med. 2004 May 27;350(22):2247-56. doi: 10.1056/NEJMoa040232. PMID: 15163774.
Crystalloid versus Hydroxyethyl Starch Trial (CHEST) Management Committee. The Crystalloid versus Hydroxyethyl Starch Trial: protocol for a multi-centre randomised controlled trial of fluid resuscitation with 6% hydroxyethyl starch (130/0.4) compared to 0.9% sodium chloride (saline) in intensive care patients on mortality. Intensive Care Med. 2011 May;37(5):816-23. doi: 10.1007/s00134-010-2117-9. Epub 2011 Feb 10. PMID: 21308360.

[x] Vasopressors: National Department of Health: Affordable Medicines, EDP-Adult Hospital level. Medicine Review: Vasopressors, inotropes as monotherapy or in combination, April 2023. http://www.health.gov.za/. https://accessmedicine.mhmedical.com/content.aspx?bookid=1944&sectionid=143516493)
Evans L, Rhodes A, Alhazzani W, Antonelli M, Coopersmith CM, French C, Machado FR, Mcintyre L, Ostermann M, Prescott HC, Schorr C, Simpson S, Wiersinga WJ, Alshamsi F, Angus DC, Arabi Y, Azevedo L, Beale R, Beilman G, Belley-Cote E, Burry L, Cecconi M, Centofanti J, Coz Yataco A, De Waele J, Dellinger RP, Doi K, Du B, Estenssoro E, Ferrer R, Gomersall C, Hodgson C, Hylander Møller M, Iwashyna T, Jacob S, Kleinpell R, Klompas M, Koh Y, Kumar A, Kwizera A, Lobo S, Masur H, McGloughlin S, Mehta S, Mehta Y, Mer M, Nunnally M, Oczkowski S, Osborn T, Papathanassoglou E, Perner A, Puskarich M, Roberts J, Schweickert W, Seckel M, Sevransky J, Sprung CL, Welte T, Zimmerman J, Levy M. Surviving Sepsis Campaign: International Guidelines for Management of Sepsis and Septic Shock 2021. Crit Care Med. 2021 Nov 1;49(11):e1063-e1143. doi: 10.1097/CCM.0000000000005337. PMID: 34605781.
xi Dobuatamine, IV: South African Medicines Formulary. 14th Edition. Division of Clinical Pharmacology. University of Cape Town. 2022.
Dobutamine: MCC registered South African package insert: Pharmaplan Cardiject® powder for IV infusion, 250 mg/vial.
National Department of Health: National Department of Health: Essential Drugs Programme. Adult Hospital level STGs and EML. Chapter 20: Emergencies and Injuries.
[xii] Acute Kidney Injury: Ostermann M, Wu V, Sokolov D, Lumlertgul N. Definitions of acute renal dysfunction: an evolving clinical and biomarker paradigm. Curr Opin Crit Care. 2021 Dec;27(6):553–9
[xiii] Staging/Severity of Acute Kidney Injury: Kidney Disease: Improving Global Outcomes (KDIGO). Acute Kidney Injury (AKI). 2012 Kidney Disease: Improving Global Outcomes (KDIGO) Clinical Practice Guideline for Acute Kidney Injury (AKI). 2012. Available at: https://kdigo.org/guidelines/acute-kidney-injury/
[xiv] Protein (Nutrition): Fiaccadori E, Sabatino A, Barazzoni R, Carrero JJ, Cupisti A, De Waele E, Jonckheer J, Singer P, Cuerda C. ESPEN guideline on clinical nutrition in hospitalized patients with acute or chronic kidney disease. Clin Nutr. 2021 Apr;40(4):1644-1668. doi: 10.1016/j.clnu.2021.01.028. Epub 2021 Feb 9. PMID: 33640205.
National Department of Health. Directorate: Nutrition. National Renal Nutrition Practice Guidelines for Adults. June 2018. http://www.health.gov.za/.
[xv]Kidney Replacement Therapy (Description) Hoste, E.A., Bagshaw, S.M., Bellomo, R., Cely, C.M., Colman, R., Cruz, D.N., Edipidis, K., Forni, L.G., Gomersall, C.D., Govil, D. and Honoré, P.M., 2015. Epidemiology of acute kidney injury in critically ill patients: the multinational AKI-EPI study. Intensive care medicine, 41, pp.1411-1423.oannidis M, Oudemans-van Straaten HM. Clinical review: Patency of the circuit in continuous renal replacement therapy. Crit Care. 2007;11(4):218. doi: 10.1186/cc5937. PMID: 17634148; PMCID: PMC2206533.
Bellomo R, Ronco C. Anticoagulation during CRRT. In: Bellomo R, Baldwin I, Ronco C, Golper T., editors. Atlas of haemofiltration. Sydney: W.B. Saunders; 2002. pp. 63–68.
Unfractionated Heparin: South African Medicines Formulary. 14th Edition. Division of Clinical Pharmacology. University of Cape Town. 2022.
[xvi]Joannidis M, Oudemans-van Straaten HM. Clinical review: Patency of the circuit in continuous renal replacement therapy. Crit Care. 2007;11(4):218. doi: 10.1186/cc5937. PMID: 17634148; PMCID: PMC2206533.
Bellomo R, Ronco C. Anticoagulation during CRRT. In: Bellomo R, Baldwin I, Ronco C, Golper T., editors. Atlas of haemofiltration. Sydney: W.B. Saunders; 2002. pp. 63–68.
Unfractionated Heparin: South African Medicines Formulary. 14th Edition. Division of Clinical Pharmacology. University of Cape Town. 2022.
[xvii]Joannidis M, Oudemans-van Straaten HM. Clinical review: Patency of the circuit in continuous renal replacement therapy. Crit Care. 2007;11(4):218. doi: 10.1186/cc5937. PMID: 17634148; PMCID: PMC2206533.
Bellomo R, Ronco C. Anticoagulation during CRRT. In: Bellomo R, Baldwin I, Ronco C, Golper T., editors. Atlas of haemofiltration. Sydney: W.B. Saunders; 2002. pp. 63–68.
Enoxaparin, SC: South African Medicines Formulary. 14th Edition. Division of Clinical Pharmacology. University of Cape Town. 2022.
[xviii] Low molecular weight heparin (first line option - prophylaxis): National Department of Health: Affordable Medicines, EDPAdult Hospital Level. Medicine Review LMWH vs. UFH for the prophylaxis and treatment of venous thromboembolism and acute coronary syndromes, April 2018. http://www.health.gov.za/
Low molecular weight heparin (first line option - prophylaxis): Junqueira DR, Zorzela LM, Perini E. Unfractionated heparin versus low molecular weight heparins for avoiding heparin-induced thrombocytopenia in postoperative patients. Cochrane Database Syst Rev. 2017 Apr 21;4:CD007557. https://www.ncbi.nlm.nih.gov/pubmed/28431186
Low molecular weight heparin (first line option - prophylaxis): Wein L, Wein S, Haas SJ, Shaw J, Krum H. Pharmacological venous thromboembolism prophylaxis in hospitalized medical patients: a meta-analysis of randomized controlled trials. Arch Intern Med. 2007 Jul 23;167(14):147686.https://www.ncbi.nlm.nih.gov/pubmed/17646601
Low molecular weight heparin (first line option - prophylaxis): National Department of Health: Affordable Medicines, EDPAdult

Enoxaparin, SC: South African Medicines Formulary. 14th Edition. Division of Clinical Pharmacology. University of Cape Town. 2022.
[xix] Unfractionated Heparin: South African Medicines Formulary. 14th Edition. Division of Clinical Pharmacology. University of Cape Town. 2022.
Low molecular weight heparin (first line option - prophylaxis): National Department of Health: Affordable Medicines, EDPAdult Hospital Level. Medicine Review LMWH vs. UFH for the prophylaxis and treatment of venous thromboembolism and acute coronary syndromes, April 2018. http://www.health.gov.za/
[xx] Red Cell Transfusions: Wise RD, de Vasconcellos K, Gopalan PD, Ahmed N, Alli A, Joubert I, Kabambi KF, Mathiva LR, Mdladla N, Mer M, Miller M, Mrara B, Omar S, Paruk F, Richards GA, Skinner D, von Rahden R. Critical Care Society of Southern Africa adult patient blood management guidelines: 2019. Round-table meeting, CCSSA Congress, Durban, 2018. South Afr J Crit Care 2020;36(1):2-19. https://doi.org/10.7196/SAJCC.2020.v36i1.440.
[xxi] van Baarle FLF, van de Weerdt EK, van der Velden WJFM, Ruiterkamp RA, Tuinman PR, Ypma PF, van den Bergh WM, Demandt AMP, Kerver ED, Jansen AJG, Westerweel PE, Arbous SM, Determann RM, van Mook WNKA, Koeman M, Mäkelburg ABU, van Lienden KP, Binnekade JM, Biemond BJ, Vlaar APJ. Platelet Transfusion before CVC Placement in Patients with Thrombocytopenia. N Engl J Med. 2023 May 25;388(21):1956-1965. doi: 10.1056/NEJMoa2214322. PMID: 37224197.
[xxii] Platelet Transfusions: Indications for platelet transfusions: Critical care society of Southern Africa. Guidelines for the provison of critical care in South Africa. July 2022. https://criticalcare.org.za/wp-content/uploads/2022/07/CCSSA-guidelines-final.pdf
[xxiii] Plasma: Wise RD, de Vasconcellos K, Gopalan PD, Ahmed N, Alli A, Joubert I, Kabambi KF, Mathiva LR, Mdladla N, Mer M, Miller M, Mrara B, Omar S, Paruk F, Richards GA, Skinner D, von Rahden R. Critical Care Society of Southern Africa adult patient blood management guidelines: 2019. Round-table meeting, CCSSA Congress, Durban, 2018. South Afr J Crit Care 2020;36(1):2-19. https://doi.org/10.7196/SAJCC.2020.v36i1.440.
[xxiv] Cryoprecipitate WCBS. Clinical guidelines - Western Cape Blood Service [Internet]. Western Cape Blood Service - Do something remarkable. 2020 [cited 2023 Nov 22]. Available from: https://www.wcbs.org.za/clinical-information/clinical-guidelines/
[xxv] Tranexamic Acid (IV): Tranexamic acid, IV: CRASH-2 trial collaborators: Shakur H et al. Effects of tranexamic acid on death, vascular occlusive events, and blood transfusion in trauma patients with significant haemorrhage (CRASH-2): a randomised, placebo-controlled trial. Lancet. 2010; 376:23-32. https://www.ncbi.nlm.nih.gov/pubmed/20554319
Roberts I et al. The importance of early treatment with tranexamic acid in bleedingtrauma patients: an exploratory analysis of the CRASH-2 randomised controlled trial. Lancet. 2011; 377:1096-1101.
Ker K, Roberts I, Shakur H, Coats TJ. Antifibrinolytic drugs for acute traumatic injury. Cochrane Database Syst Rev. 2015 May 9;(5):CD004896. https://www.ncbi.nlm.nih.gov/pubmed/25956410
[xxvi] Tranexamic Acid (IV): South African Medicines Formulary. 14th Edition. Division of Clinical Pharmacology. University of Cape Town. 2022.
Tranexamic acid, IV: National Department of Health: Affordable Medicines, EDP-Adult Hospital level. Medicine Review: Tranexamic acid, IV, for management of post partum haemmhorhage in pregnant women, 11 October 2017. http://www.health.gov.za/
[xxvii] Massive Transfusion Protocol (Definitions): Shah A, Kerner V, Stanworth SJ, Agarwal S. Major haemorrhage: past, present and future. Anaesthesia. 2023 Jan;78(1):93-104. doi: 10.1111/anae.15866. Epub 2022 Sep 12. PMID: 36089857; PMCID: PMC10087440.
[xxviii] Neuro-psychological Support: Reade MC, Finfer S. Sedation and Delirium in the Intensive Care Unit. N Engl J Med. 2014 Jan 30;370(5):444–54.
[xxix]Neuro-psychological Support: Devlin JW, Skrobik Y, Gélinas C, Needham DM, Slooter AJC, Pandharipande PP, et al. Clinical Practice Guidelines for the Prevention and Management of Pain, Agitation/Sedation, Delirium, Immobility, and Sleep Disruption in Adult Patients in the ICU. Crit Care Med. 2018 Sep;46(9):e825–73.
Payen JF, Bru O, Bosson JL, Lagrasta A, Novel E, Deschaux I, et al. Assessing pain in critically ill sedated patients by using a behavioral pain scale. Crit Care Med. 2001 Dec;29(12):2258–63.
[xxx]Neuro-psychological Support: Khan BA, Perkins AJ, Gao S, Hui SL, Campbell NL, Farber MO, et al. The CAM-ICU-7 Delirium Severity Scale: A Novel Delirium Severity Instrument for Use in the Intensive Care Unit. Crit Care Med. 2017 May;45(5):851–7.
[xxxi]Ketamine: Ketamine, IV: National Department of Health: Affordable Medicines, EDP-Adult Hospital level. Medicine Review: Ketamine (adjunctive or monotherapy) for analgosedation in traumatised intubated adults on mechanical ventilation, September 2022. https://www.knowledgehub.org.za/content/standard-treatment-guidelines-and-essential-medicines-list
[xxxii]Neuro-psychologicl Support: Fuchs B, Bellamy C. Sedative-analgesic medications in critically ill adults:Selection, initiation, maintenance, and withdrawal. In: UpToDate, Post TW (Ed), UpToDate, Waltham, MA. (Accessed on April 04, 2022.)
Sessler CN, Gosnell MS, Grap MJ, Brophy GM, O'Neal PV, Keane KA, et al. The Richmond Agitation-Sedation Scale: validity and reliability in adult intensive care unit patients. Am J Respir Crit Care Med. 2002 Nov 15;166(10):1338–44.

National Department of Health: National Department of Health: Essential Drugs Programme. Adult Hospital level STGs and EML. Chapter 12: Anaesthesiology And Intensive Care..
National Department of Health: National Department of Health: Essential Drugs Programme. Adult Hospital level STGs and EML. Chapter 23: Sedation.
Morphine, IV (dosing): South African Medicines Formulary. 12th Edition. Division of Clinical Pharmacology. University of Cape Town, 2016.
Fentanyl, IV: The South African Society of Anaesthesiologists. South African Acute Pain Guidelines. SAJAA 2009;15(6):1-120. http://www.sasaweb.com/content/images/SASA_Pain_Guidelines.pdf
Fentanyl, IV: Scholz J, Steinfath M, Schulz M. Clinical pharmacokinetics of alfentanil, fentanyl and sufentanil. An update. Clin Pharmacokinet. 1996 Oct;31(4):275-92.
http://www.ncbi.nlm.nih.gov/pubmed/8896944Ketamine, IV: McNicol ED, Schumann R, Haroutounian S. A systematic review and meta-analysis of ketamine for the prevention of persistent post-surgical pain. Acta Anaesthesiol Scand. 2014 Nov;58(10):1199-213. http://www.ncbi.nlm.nih.gov/pubmed/25060512
Ketamine, IV: Brinck EC, Tiippana E, Heesen M, Bell RF, Straube S, Moore RA, Kontinen V. Perioperative intravenous ketamine for acute postoperative pain in adults. Cochrane Database Syst Rev. 2018 Dec 20;12:CD012033. https://www.ncbi.nlm.nih.gov/pubmed/30570761xxxii Ketamine, IV: Brinck EC, Tiippana E, Heesen M, Bell RF, Straube S, Moore RA, Kontinen V. Perioperative intravenous ketamine for acute postoperative pain in adults. Cochrane Database Syst Rev. 2018 Dec 20;12:CD012033. https://www.ncbi.nlm.nih.gov/pubmed/30570761

Tramadol, IV: Houmes RJ, Voets MA, Verkaaik A, Erdmann W, Lachmann B. Efficacy and safety of tramadol versus morphine for moderate and severe postoperative pain with special regard to respiratory depression. Anesth Analg. 1992 Apr;74(4):510-4. http://www.ncbi.nlm.nih.gov/pubmed/1554117
[xxxii]Tramadol, IV: National Department of Health, Essential Drugs Programme. Medicine review: Tramadolol, IV July 2015. http://health.gov.za/
[xxxiii] Neuro-psychological Support: Khan BA, Perkins AJ, Gao S, Hui SL, Campbell NL, Farber MO, et al. The CAM-ICU-7 Delirium Severity Scale: A Novel Delirium Severity Instrument for Use in the Intensive Care Unit. Crit Care Med. 2017 May;45(5):851–7.
[xxxiv]Neuro-psychological Support: Khan BA, Perkins AJ, Gao S, Hui SL, Campbell NL, Farber MO, et al. The CAM-ICU-7 Delirium Severity Scale: A Novel Delirium Severity Instrument for Use in the Intensive Care Unit. Crit Care Med. 2017 May;45(5):851–7.
[xxxv]Sedation Medicines: South African Medicines Formulary. 14th Edition. Division of Clinical Pharmacology. University of Cape Town. 2022.
Propofol Dosage. https://www.drugs.com/dosage/propofol.html
[xxxvi]Delirium in Critical Care: Burry et al. (2019) Pharmacological interventions for the treatment of delirium in critically ill adults.Cochrane Database of Systematic Reviews, Issue 9. Art. No.: CD011749.
DOI: 10.1002/14651858.CD011749.pub2.
Devlin et al. (2018) Clinical Practice Guidelines for the Prevention and Management of Pain, Agitation/Sedation, Delirium, Immobility, and Sleep Disruption in Adult Patients in the ICU. Critical Care Medicine. DOI: 10.1097/CCM.0000000000003299
Stollings et al. (2021) Delirium in critical illness: clinical manifestations, outcomes, and management. Intensive Care Med 47:1089–1103
DOI: 10.1007/s00134-021-06503-1
[xxxvii] Neuro-psychologicl Support: Khan BA, Perkins AJ, Gao S, Hui SL, Campbell NL, Farber MO, Chlan LL, Boustani MA. The Confusion Assessment Method for the ICU-7 Delirium Severity Scale: A Novel Delirium Severity Instrument for Use in the ICU. Crit Care Med. 2017 May;45(5):851-857. doi: 10.1097/CCM.0000000000002368. PMID: 28263192; PMCID: PMC5392153..
[xxxviii].National Department of Health. Directorate: Nutrition. National Parenteral Nutrition Practice. Guidelines for Adults. 2016. http://www.health.gov.za/.
National Department of Health. Directorate: Nutrition. National Enteral Nutrition Practice. Guidelines for Adults. 2016. http://www.health.gov.za/.
[xxxix]Stress Ulcer Prophylaxis: Mohebbi L, Hesch K. Stress ulcer prophylaxis in the intensive care unit. Proc (Bayl Univ Med Cent). 2009 Oct;22(4):373-6. doi: 10.1080/08998280.2009.11928562. PMID: 21240306; PMCID: PMC2760176.
Bardou, M., Quenot, JP. & Barkun, A. Stress-related mucosal disease in the critically ill patient. Nat Rev Gastroenterol Hepatol 12, 98–107 (2015). https://doi.org/10.1038/nrgastro.2014.235
[xl]Pantoprazole IV Tsoi KK, Hirai HW, Sung JJ. Meta-analysis: comparison of oral vs. intravenous proton pump inhibitors in patients with peptic ulcer bleeding. Aliment Pharmacol Ther. 2013 Oct;38(7):721-8. doi: 10.1111/apt.12441. Epub 2013 Aug 5. PMID: 23915096.
National Institute for Health and Care Excellence. Gastro-oesophageal reflux disease and dyspepsia in adults:investigation and management. 2014.
https://www.nice.org.uk/guidance/cg184/resources/gastrooesophageal-reflux-disease-and-dyspepsia-in-adults-investigation-and-management-pdf-35109812699845
[xli] PH Analysis (Aspirate): Moore M, Thomson R. Confirmation of nasogastric tube placement in critical care. Crit Care. 2013;17(Suppl 2):P244. doi: 10.1186/cc12182. Epub 2013 Mar 19. PMCID: PMC3642739.

[xlii] Diarrrhoea (Description): Dionne JC, Mbuagbaw L. Diarrhea in the critically ill: definitions, epidemiology, risk factors and outcomes. Curr Opin Crit Care. 2023 Apr 1;29(2):138-144. doi: 10.1097/MCC.0000000000001024. Epub 2023 Feb 22. PMID: 36825593..
[xliii] Acute Severe Pancreatitis (Description): Finkenstedt, A., Jaber, S. & Joannidis, M. Ten tips to manage severe acute pancreatitis in an intensive care unit. *Intensive Care Med* 49, 1127–1130 (2023). https://doi.org/10.1007/s00134-023-07121-9
Leppäniemi A, Tolonen M, Tarasconi A, Segovia-Lohse H, Gamberini E, Kirkpatrick AW, Ball CG, Parry N, Sartelli M, Wolbrink D, van Goor H, Baiocchi G, Ansaloni L, Biffl W, Coccolini F, Di Saverio S, Kluger Y, Moore E, Catena F. 2019 WSES guidelines for the management of severe acute pancreatitis. World J Emerg Surg. 2019 Jun 13;14:27. doi: 10.1186/s13017-019-0247-0. PMID: 31210778; PMCID: PMC6567462..
[xliv] Acute Cholecystitis (Description): Finkenstedt, A., Jaber, S. & Joannidis, M. Ten tips to manage severe acute pancreatitis in an intensive care unit. *Intensive Care Med* 49, 1127–1130 (2023). https://doi.org/10.1007/s00134-023-07121-9
Leppäniemi A, Tolonen M, Tarasconi A, Segovia-Lohse H, Gamberini E, Kirkpatrick AW, Ball CG, Parry N, Sartelli M, Wolbrink D, van Goor H, Baiocchi G, Ansaloni L, Biffl W, Coccolini F, Di Saverio S, Kluger Y, Moore E, Catena F. 2019 WSES guidelines for the management of severe acute pancreatitis. World J Emerg Surg. 2019 Jun 13;14:27. doi: 10.1186/s13017-019-0247-0. PMID: 31210778; PMCID: PMC6567462
[xlv] Abdominal Compartment Syndrome (Description) Harris, H. & Smith, C. J. (2013). Understanding abdominal compartment syndrome. Nursing Critical Care, 8 (3), 45-47. doi: 10.1097/01.CCN.0000429385.10473.7f.
Rajasurya V, Surani S. Abdominal compartment syndrome: Often overlooked conditions in medical intensive care units. World J Gastroenterol. 2020 Jan 21;26(3):266-278. doi: 10.3748/wjg.v26.i3.266. PMID: 31988588; PMCID: PMC6969886.
Bailey, J., Shapiro, M.J. Abdominal compartment syndrome . Crit Care 4, 23 (2000). https://doi.org/10.1186/cc646
[xlvi] Atenolol (oral): South African Medicines Formulary. 14th Edition. Division of Clinical Pharmacology. University of Cape Town. 2022.
[xlvii] Myxoedema Coma (Description) Acharya R, Cheng C, Bourgeois M, Masoud J, McCray E. Myxedema Coma: A Forgotten Medical Emergency With a Precipitous Onset. Cureus. 2020 Sep 16;12(9):e10478. doi: 10.7759/cureus.10478. PMID: 33083180; PMCID: PMC7567317.
Mohsen. Myxedema Coma or Crisis: Practice Essentials, Pathophysiology, Epidemiology [Internet]. Medscape.com. Medscape; 2023 [cited 2023 Nov 17]. Available from: https://emedicine.medscape.com/article/123577-overview
[xlviii] Myxoedema Coma Pinar, A.U. (2017). Management of Myxedema Coma. In: Hyzy, R. (eds) Evidence-Based Critical Care. Springer, Cham. https://doi.org/10.1007/978-3-319-43341-7_51
xlix Myxoedema Coma (Thyroid hormone replacement) South African Medicines Formulary. 14th Edition. Division of Clinical Pharmacology. University of Cape Town. 2022..
[l] Corticosteroid: South African Medicines Formulary. 14th Edition. Division of Clinical Pharmacology. University of Cape Town. 2022..
[li] Glucose Levels: Johan Mårtensson, Moritoki Egi, Rinaldo Bellomo, Chapter 79 - Blood Glucose Control in Critical Care,Editor(s): Claudio Ronco, Rinaldo Bellomo, John A. Kellum, Zaccaria Ricci, Critical Care Nephrology (Third Edition), Elsevier, 2019, Pages 464-469.e2, ISBN 9780323449427, https://doi.org/10.1016/B978-0-323-44942-7.00079-0.
[lii] Glucagon: South African Medicines Formulary. 14th Edition. Division of Clinical Pharmacology. University of Cape Town. 2022..
[liii] Hyperglycaemia (Description) Chawla, Rajeev; Gangopadhyay, Kalyan Kumar1; Lathia, Tejal Bipin2; Punyani, Hitesh3; Kanungo, Alok4; Sahoo, Abhay Kumar5; Seshadri, Krishna G.6. Management of Hyperglycemia in Critical Care. Journal of Diabetology 13(1):p 33-42, Jan–Mar 2022. | DOI: 10.4103/jod.jod_69_21.
[liv] Definition: Sepsis: Singer M, Deutschman CS, Seymour CW, Shankar-Hari M, Annane D, Bauer M, Bellomo R, Bernard GR, Chiche JD, Coopersmith CM, Hotchkiss RS, Levy MM, Marshall JC, Martin GS, Opal SM, Rubenfeld GD, van der Poll T, Vincent JL, Angus DC. The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). JAMA. 2016 Feb 23;315(8):801-10. doi: 10.1001/jama.2016.0287. PMID: 26903338; PMCID: PMC4968574.
[lv] SOFA SCORE; Vincent JL, Moreno R, Takala J, et al. The SOFA (Sepsis-related Organ Failure Assessment) score to describe organ dysfunction/failure. Intensive Care Med. 1996;22:707–710.
Gyawali B, Ramakrishna K, Dhamoon AS. Sepsis: The evolution in definition, pathophysiology, and management. SAGE Open Med. 2019 Mar 21;7:2050312119835043. doi: 10.1177/2050312119835043
[lvi] Balanced salt solutions: NDoH, Affordable Medicines, EDP-Adult Hospital level. Medicine Review: Ringer Lactate for resuscitation in adults, updated review, August 2019. http://www.health.gov.za/
[lvii] Sepsis in ICU (Vasopressors): National Department of Health: Affordable Medicines, EDP-Adult Hospital level. Medicine Review: Vasopressors, inotropes as monotherapy or in combination, April 2023. http://www.health.gov.za/.
https://accessmedicine.mhmedical.com/content.aspx?bookid=1944&sectionid=143516493)
Evans L, Rhodes A, Alhazzani W, Antonelli M, Coopersmith CM, French C, Machado FR, Mcintyre L, Ostermann M, Prescott HC, Schorr C, Simpson S, Wiersinga WJ, Alshamsi F, Angus DC, Arabi Y, Azevedo L,

Beale R, Beilman G, Belley-Cote E, Burry L, Cecconi M, Centofanti J, Coz Yataco A, De Waele J, Dellinger RP, Doi K, Du B, Estenssoro E, Ferrer R, Gomersall C, Hodgson C, Hylander Møller M, Iwashyna T, Jacob S, Kleinpell R, Klompas M, Koh Y, Kumar A, Kwizera A, Lobo S, Masur H, McGloughlin S, Mehta S, Mehta Y, Mer M, Nunnally M, Oczkowski S, Osborn T, Papathanassoglou E, Perner A, Puskarich M, Roberts J, Schweickert W, Seckel M, Sevransky J, Sprung CL, Welte T, Zimmerman J, Levy M. Surviving Sepsis Campaign: International Guidelines for Management of Sepsis and Septic Shock 2021. Crit Care Med. 2021 Nov 1;49(11):e1063-e1143. doi: 10.1097/CCM.0000000000005337. PMID: 34605781.

[lviii] Sepsis in ICU (Dobutamine): Evans L, Rhodes A, Alhazzani W, Antonelli M, Coopersmith CM, French C, Machado FR, Mcintyre L, Ostermann M, Prescott HC, Schorr C, Simpson S, Wiersinga WJ, Alshamsi F, Angus DC, Arabi Y, Azevedo L, Beale R, Beilman G, Belley-Cote E, Burry L, Cecconi M, Centofanti J, Coz Yataco A, De Waele J, Dellinger RP, Doi K, Du B, Estenssoro E, Ferrer R, Gomersall C, Hodgson C, Hylander Møller M, Iwashyna T, Jacob S, Kleinpell R, Klompas M, Koh Y, Kumar A, Kwizera A, Lobo S, Masur H, McGloughlin S, Mehta S, Mehta Y, Mer M, Nunnally M, Oczkowski S, Osborn T, Papathanassoglou E, Perner A, Puskarich M, Roberts J, Schweickert W, Seckel M, Sevransky J, Sprung CL, Welte T, Zimmerman J, Levy M. Surviving Sepsis Campaign: International Guidelines for Management of Sepsis and Septic Shock 2021. Crit Care Med. 2021 Nov 1;49(11):e1063-e1143. doi: 10.1097/CCM.0000000000005337. PMID: 34605781.

South African Medicines Formulary. 14th Edition. Division of Clinical Pharmacology. University of Cape Town. 2022

[lix] Sepsis in ICU (Vasopressors): National Department of Health: Affordable Medicines, EDP-Adult Hospital level. Medicine Review: Vasopressors, inotropes as monotherapy or in combination, April 2023. http://www.health.gov.za/.
https://accessmedicine.mhmedical.com/content.aspx?bookid=1944&sectionid=143516493)
Evans L, Rhodes A, Alhazzani W, Antonelli M, Coopersmith CM, French C, Machado FR, Mcintyre L, Ostermann M, Prescott HC, Schorr C, Simpson S, Wiersinga WJ, Alshamsi F, Angus DC, Arabi Y, Azevedo L, Beale R, Beilman G, Belley-Cote E, Burry L, Cecconi M, Centofanti J, Coz Yataco A, De Waele J, Dellinger RP, Doi K, Du B, Estenssoro E, Ferrer R, Gomersall C, Hodgson C, Hylander Møller M, Iwashyna T, Jacob S, Kleinpell R, Klompas M, Koh Y, Kumar A, Kwizera A, Lobo S, Masur H, McGloughlin S, Mehta S, Mehta Y, Mer M, Nunnally M, Oczkowski S, Osborn T, Papathanassoglou E, Perner A, Puskarich M, Roberts J, Schweickert W, Seckel M, Sevransky J, Sprung CL, Welte T, Zimmerman J, Levy M. Surviving Sepsis Campaign: International Guidelines for Management of Sepsis and Septic Shock 2021. Crit Care Med. 2021 Nov 1;49(11):e1063-e1143. doi: 10.1097/CCM.0000000000005337. PMID: 34605781.

[lx] Amoxicillin-Clavulanic Acid (Prolonged Infusions): Fawaz S, Dixon B, Barton S, Mohamed A, Nabhani-Gebara S. Suitability of Amoxicillin-Clavulanic Acid for Administration via Prolonged Infusion. Drug Des Devel Ther. 2020 Jan 10;14:103-109.
doi:10.2147/DDDT.S230459.https://accessmedicine.mhmedical.com/content.aspx?bookid=1944&sectionid=143516493)

[lxi] Meropenem (Dosing Interval): Lertwattanachai, T., Montakantikul, P., Tangsujaritvijit, V. et al. Clinical outcomes of empirical high-dose meropenem in critically ill patients with sepsis and septic shock: a randomized controlled trial. j intensive care 8, 26 (2020). https://doi.org/10.1186/s40560-020-00442-7

[lxii]Ceftazidime-Avibactam: National Department of Health: Affordable Medicines, EDP-Adult Hospital level. Medicine Review: Ceftazidime-avibactam for the treatment of carbapenem-resistant Enterobacterales (CRE) bacteraemia, July2023 (Updated September 2023). http://www.health.gov.za/.
https://accessmedicine.mhmedical.com/content.aspx?bookid=1944&sectionid=143516493

[lxiii] Empiric antifingal therapy: Pappas PG, Kauffman CA, Andes DR, Clancy CJ, Marr KA, Ostrosky-Zeichner L, Reboli AC, Schuster MG, Vazquez JA, Walsh TJ, Zaoutis TE, Sobel JD. Clinical Practice Guideline for the Management of Candidiasis: 2016 Update by the Infectious Diseases Society of America. Clin Infect Dis. 2016 Feb 15;62(4):e1-50. doi: 10.1093/cid/civ933. Epub 2015 Dec 16. PMID: 26679628; PMCID: PMC4725385.

[lxiv] Hydrocortisone (IV): Evans L, Rhodes A, Alhazzani W, Antonelli M, Coopersmith CM, French C, Machado FR, Mcintyre L, Ostermann M, Prescott HC, Schorr C, Simpson S, Wiersinga WJ, Alshamsi F, Angus DC, Arabi Y, Azevedo L, Beale R, Beilman G, Belley-Cote E, Burry L, Cecconi M, Centofanti J, Coz Yataco A, De Waele J, Dellinger RP, Doi K, Du B, Estenssoro E, Ferrer R, Gomersall C, Hodgson C, Hylander Møller M, Iwashyna T, Jacob S, Kleinpell R, Klompas M, Koh Y, Kumar A, Kwizera A, Lobo S, Masur H, McGloughlin S, Mehta S, Mehta Y, Mer M, Nunnally M, Oczkowski S, Osborn T, Papathanassoglou E, Perner A, Puskarich M, Roberts J, Schweickert W, Seckel M, Sevransky J, Sprung CL, Welte T, Zimmerman J, Levy M. Surviving Sepsis Campaign: International Guidelines for Management of Sepsis and Septic Shock 2021. Crit Care Med. 2021 Nov 1;49(11):e1063-e1143. doi: 10.1097/CCM.0000000000005337. PMID: 34605781.

[lxv] End of Life Care: Paruk F, Kissoon N, Hartog CS, Hodgson RE, Lipman J, Guidet B, Du B, Argent A. The Durban World Congress Ethics Round Table: III. Withdrawing Mechanical ventilation- The approach should be individualized. J Crit Care. 2014 Jun 4. pii: S0883-9441(14)00223-8. doi: 10.1016/j.jcrc.2014.05.022.
End of Life Care: Joynt GM, Lipman J, Hartog C, Guidet B, Paruk F, Feldman C, Kissoon N, Sprung CL. The Durban World Congress Ethics Round Table IV: Health care professional end-of-life decision making. J Crit Care. 2015 Apr;30(2):224-30. doi: 10.1016/j.jcrc.2014.10.011

[lxv] End of Life Care: Sprung CL, Paruk F, Kissoon N, Hartog CS, Lipman J, Du B, Argent A, Hodgson E, Guidet B, Groeneveld ABJ and Feldman C. The Durban World Congress Ethics Round Table Conference

Report: I. Differences between withholding and withdrawing life-sustaining treatments. Journal of Critical Care 2014 Dec;29(6):890-5. doi: 10.1016/j.jcrc.2014.06.022
[lxvi] End of Life Care: Thomson D, Joubert I, K De Vasconcellos, F Paruk, S Mokogong, R Mathivha, et al. South African Guidelines on the Determination of Death. South African Medical Journal [Internet]. 2014 [cited 2023 Nov 21];111(4b):367–80. Available from: http://www.samj.org.za/index.php/samj/article/view/13264/9746
[lxvii] End of Life Care: Thomson D, Joubert I, K De Vasconcellos, F Paruk, S Mokogong, R Mathivha, et al. South African Guidelines on the Determination of Death. South African Medical Journal [Internet]. 2014 [cited 2023 Nov 21];111(4b):367–80. Available from: http://www.samj.org.za/index.php/samj/article/view/13264/9746

CHAPTER 24
MEDICINES USED IN PALLIATIVE CARE

PALLIATIVE CARE

Palliative care is an approach that improves the quality of life of patients and their families' facing problems associated with life-threatening illness, regardless of whether or not they also receive life-prolonging treatment.

Palliative care requires a multidisciplinary approach and aims to address physical, psychosocial, and spiritual problems.

Life threatening illnesses are where death is expected to be a direct consequence of the specified illness.
Analysis of available evidence suggested 11 common symptoms occurring in the advanced stages and end of life stages: anorexia, anxiety, constipation, delirium, depression, diarrhoea, dyspnoea, fatigue, nausea and vomiting, pain and respiratory tract secretions.
All symptoms should be managed by a multi-disciplinary team to ensure a holistic approach.

Note: Please be advised that the recommendations in this chapter are directed at treating common symptoms alongside disease directed care and symptoms associated with end-of-life care.

The SPICT^{TM}-SA is a generic tool (https://www.spict.org.uk/the-spict/spict-sa/), designed for the South African setting, to help identify adults with advanced life-limiting illnesses when the best available and appropriate treatment has been given and their condition continues to deteriorate.

LoE:IVb[i]

Always refer to the latest National Guidelines on Palliative Care.

For management of pain in palliative care see Chapter 25: Pain.

24.1 GASTROINTESTINAL CONDITIONS

24.1.1 ANOREXIA AND CACHEXIA

R63.0/R63.4/R64 + (Z51.5)

DESCRIPTION

Anorexia/cachexia syndrome is a complex metabolic process found in many end-stage illnesses. It is characterised by loss of appetite, weight loss and

muscle wasting, and cannot be fully reversed by conventional nutritional support. It may impact significantly on the quality of life of patients, leading to increased anxiety and distress for both patients as well as family.

GENERAL MEASURES

Reduced food and fluid intake is expected at the end of life, and treatment of anorexia and weight loss may not be appropriate if these symptoms are not having a direct impact on quality of life. This should be explained to caregivers and family.

Management of anorexia and weight loss includes identification and, if appropriate, treatment of possible underlying cause(s). It may include the use of pharmacological and non-pharmacological treatment approaches.

Identify reversible problems that may contribute to or exacerbate anorexia/ cachexia including:

- Pain, nausea, heartburn, dyspnoea, gastritis, depression, constipation anxiety dysphagia, medication and fatigue
- Oral problems e.g. dry mouth, ulcers, candidiasis, etc.
- Odours e.g. fungating lesions, cooking smells, incontinence etc.
- Delayed gastric emptying due to local disease, autonomic neuropathy with early satiety and vomiting of undigested foods

If appropriate, moderate exercise must be encouraged, along with pacing of activities and good sleep hygiene.

Nutritional advice includes eating small amounts of enjoyable food frequently.

MEDICINE TREATMENT

If the anorexia and/ cachexia contributes significantly to decreased quality of life and the patient has a short life expectancy.

- Corticosteroids (intermediate-acting) e.g.:
- Prednisone, oral, 0.5 mg/kg (e.g. 20 to 30 mg) daily.
  - The effect may be rapid but usually decreases after 3 to 4 weeks.
  - If there is no benefit after 1 week, stop the treatment.

LoE:IIb[a]

If symptoms of reflux or gastritis: see Section 1.1.3: Gastro-oesophageal reflux disease and dyspepsia.

If gastroparesis is present, see Section 8.7.1: Diabetic neuropathies.

24.1.2 CONSTIPATION

K59.0 + (Z51.5)

DESCRIPTION

Constipation is the passage of small, hard faeces infrequently and with difficulty. Individuals vary in the weight they give to the different components of this definition when assessing their own constipation and may introduce

other factors, such as pain and discomfort when defecating, flatulence, bloating or a sensation of incomplete evacuation. Constipation may also be secondary to other conditions e.g. dehydration, immobility poor diet, anorexia, tumour compressing bowel wall or hypercalcaemia.

GENERAL MEASURES

Ensure privacy and comfort to allow a patient to defecate normally.
Increase fluid intake within the patient's limits.
Encourage activity and increased mobility within the patient's limits.
Anticipate the constipating effects of pharmacological agents such as opioids, anticholinergic agents (e.g. tricyclic antidepressants), antacids, iron, 5HT3 antagonists and provide laxatives prophylactically.

MEDICINE TREATMENT

The combination of a softener and stimulant laxative is generally recommended, and the choice of laxatives should be made on an individual basis.

- Sennosides A and B, oral, 13.5 mg, 1 tablet at night.
  - In resistant cases increase to 2 tablets.

AND/OR *LoE:IIb[iii]*

Lactulose, oral, 15–30 mL 12–24 hourly. *LoE:IIb[iv]*

Severe constipation in patients who are unable to swallow:

- Bisacodyl, rectal, 10 mg suppository daily. *LoE:IVb[v]*

OR

Glycerine (glycerol), rectal, 1.698 mL/2.4 g suppository when necessary. *LoE:IVb*

If these therapies are not effective, other options could be considered.

Note: Manual removal should only be undertaken if the patient has received adequate pain relief and sedation, if relevant.

REFERRAL/CONSULTATION

If bowel obstruction is suspected refer/consult for appropriate radiological investigations and, if appropriate, surgical interventions.

24.1.2.1 TUMOUR-RELATED BOWEL OBSTRUCTION

K56.6

DESCRIPTION

Malignant bowel obstruction is a well-recognised complication of advanced cancer and is defined as symptoms, signs, and radiographic evidence of obstruction to the transit of gastrointestinal contents caused by cancer, or the consequences of anticancer therapy including surgery, chemotherapy or radiation therapy. It occurs most commonly with ovarian or colorectal cancer.

LoE:IVb[vi]

GENERAL MEASURES
Consult a surgeon to discuss potential surgical interventions before restricting management to medicine treatment. Patients and families require in depth counselling around the cause, care, further nutrition, and nasogastric tubes. Parenteral nutrition generally has no role in patients with advanced cancer.

MEDICINE TREATMENT
These patients may be difficult to manage. Consult with a palliative care provider for advice on management of patient.

To identify and contact a palliative care provider, if necessary, visit: https://palprac.org/palliative-care/find-a-provider/.

See Section 24.1.4: Nausea and Vomiting.

REFERRAL/CONSULTATION
All patients that might require surgical management must be discussed with a surgeon.
All patients who require medical management of bowel obstruction must be discussed with a palliative care provider.

24.1.3 DIARRHOEA
A09.0

See Primary Health Care chapter: Medicines for palliative care: Section 22.1.2: Diarrhoea.

24.1.4 NAUSEA AND VOMITING
R11 + (Z51.5)

GENERAL MEASURES
Treat the underlying cause and rehydrate the patient.
Identify and manage reversible causes, which include medication, hypercalcemia, constipation, uraemia, gastritis, gastroenteritis, coughing and infections.
Manage odours e.g. cooking smells and fungating wounds.

MEDICINE TREATMENT
- Metoclopramide, oral/IM/IV, 10 mg 8 hourly, 30 minutes before a meal.
- In renal impairment start with a dose of 5 mg, 8 hourly.

- Increase according to clinical response using alternate 5 mg and 10 mg doses if required.

LoE:IVb[vii]

If metoclopramide is ineffective or contra-indicated (e.g., inoperable bowel obstruction):

- Haloperidol, oral, 1.5–5 mg daily.

OR LoE:IIIb[viii]

- Olanzapine orodispersible tablet, oral or IM injection
  - Initiate 5 mg at night (2.5 mg in frail and elderly patients).
  - Titrate in increments of 2.5 mg to a maximum dose of 10 mg daily.

Monitor vital signs and beware of oversedation, neuroleptic malignant syndrome, and acute dystonia. LoE:IVb[ix]

Drug-induced parkinsonism: LoE:IVb[x]

ADD

- Anticholinergic agent, e.g.:
- Orphenadrine, oral, 50–150 mg daily according to individual response
  - Usual dose: 50 mg 8 hourly.
  - Maximum dose: 150 mg daily.
  - Use with caution in the elderly as it may cause confusion and urinary retention.

Note: Anticholinergic medicines (e.g. orphenadrine) should not be added prophylactically to antipsychotics to prevent extrapyramidal side effects.

If haloperidol is ineffective/ inoperable bowel obstruction:

- Promethazine, IM/IV, 12.5 to 25 mg, 4–6 hourly. LoE:IVb[xi]

Corticosteroids can decrease cerebral oedema: see Section: 14.14.1: Brain oedema due to tumours and inflammation.

REFERRAL

See Section 24.1.2.1 Tumour-related bowel obstruction
Consult a palliative care trained doctor if the vomiting persists.

24.1.5 MANAGEMENT OF CLOSE CONTACTS OF PATIENTS WITH HBV INFECTED HEPATOCELLULAR CARCINOMA

For patients with hepatocellular carcinoma caused by hepatitis B who are not on hepatitis B antiviral therapy (tenofovir/lamivudine/emtricitabine):

Screen caregivers, who are or will be in contact with bodily fluids, for hepatitis B including hepatitis B surface antigen (HBsAg) and hepatitis B surface antibody (HBsAb):

» Vaccinate non-immune individuals against hepatitis B (see Section 9.2 Adult vaccination).
» Link individuals who test positive for HBsAg to care (see Section 1.2.4.1: Hepatitis B, Acute and Sections 1.2.4.2 and 1.2.4.3: Hepatitis B, Chronic without or with HIV co-infection, respectively).
» Educate rest of family regarding the risk of infection from bodily fluids.

Consult the most recent Hepatitis Guidelines from the National Department of Health

24.2 NEUROPSYCHIATRIC CONDITIONS

24.2.1 ANXIETY

F41.0-3/ F41.8-9+ (Z51.5)

DESCRIPTION

Anxiety is defined as the apprehensive anticipation of future danger or misfortune accompanied by a feeling of dysphoria or somatic symptoms of tension. Anxiety is characterised by excessive feelings of fear, apprehension, and worry. Anxiety may be associated with symptoms of depression, poor concentration, insomnia, irritability, panic attacks, sweating, tremor and nausea. It is a common symptom in palliative care and the complex multi-causative nature of anxiety in patients with life threatening illnesses always require a multimodal approach.

GENERAL MEASURES

Address any contributing factors such as pain and dyspnoea. Consider other underlying conditions that may mimic anxiety e.g. electrolyte imbalance, hyperthyroidism, hypoxia, arrhythmias and many medicine side effects.
Assess for depression or any other previous psychiatric illness.
Include the caregivers.
Ensure the patient and caregivers have received the desired amount of information around the nature of the disease, treatment, side-effects and outcomes.
A multi-disciplinary team approach is recommended (including a spiritual carer).

MEDICINE TREATMENT

Acute management of anxiety:
<u>For an acute episode or intense prolonged anxiety:</u>

- Benzodiazepine, e.g.:
- Diazepam, oral, 2.5 to 5 mg as a single dose.
  - Repeat if required up to 12 hourly. *LoE:IIb*[xii]
  - Avoid if liver function impaired.

OR LoE:IVb[xiii]

- Lorazepam, oral, 0.5 to 1 mg, immediately.
  - Repeat as necessary to control symptoms. LoE:IVb[xiv]
  - Tablets may be crushed and administered sublingually.

LoE:IIIb[xv]

CAUTION
Benzodiazepines, especially diazepam IV, can cause respiratory depression.
Patients with liver dysfunction require lower doses.
Monitor patients closely. LoE:IVb[xvi]
In the short-term, benzodiazepines can aggravate delirium.

» In frail and elderly patients or where respiratory depression is a concern, reduce the dose by half. LoE:IVb[xvii]
» The safest route of administration is oral with the IV route having the highest risk of respiratory depression and arrest.
» Monitor vital signs closely during and after administration.
» Use haloperidol instead of benzodiazepines in patients with respiratory insufficiency.
» To avoid inappropriate repeat dosing allow at least 15 to 30 minutes for the medication to take effect. Repeated IM doses of benzodiazepines may result in toxicity owing to accumulation.

Patient unable to take oral medication/ terminal sedation required:
see Section 24.5: Sedation in palliative care.

Long-term treatment:

- SSRI e.g.:
- Fluoxetine, oral. LoE:IIb[xviii]
  - Initiate at 20 mg every alternate day for 2 weeks.
  - Increase to 20 mg daily after 2–4 weeks.
  - Delay dosage increase if increased agitation/panicked feelings occur.
  - Note: Fluoxetine is contraindicated if eGFR < 10mL/min.

LoE:IIb[xix]

OR

- Citalopram, oral.
  - Initiate at 10 mg daily for 2 weeks.
  - Then increase to 20 mg daily.

LoE:IVb[xx]

Note: Effects of SSRIs are only apparent after 2 to 3 weeks of treatment, so they should be reserved for patients where end-of-life is not imminent.

REFERRAL

Poor response to treatment.

24.2.2 DELIRIUM

F05.0-1/F05.8-9 + (Z51.5)

DESCRIPTION

Delirium (confusion) is very common in the terminal stages of advanced disease and is associated with a short prognosis. When treatment of the underlying cause(s) of delirium is not possible or unsuccessful, pharmacological management is necessary. Causal treatment may not be indicated in patients with limited prognosis and pharmacological symptomatic therapy has to be initiated without delay.

See Section 20.8: Delirium.

GENERAL MEASURES

Assess for underlying causes e.g. infection or electrolyte imbalance.
Remove factors that can agitate the patient (e.g. full bladder, thirst, pain, constipation, medicines such as opioids, steroids, benzodiazepines, withdrawal of medicines, dehydration, liver or renal impairment and cerebral tumour).
Reduce polypharmacy.
Where appropriate, ensure adequate fluid and nutritional intake (not indicated in the pre-terminal stage).
Mobilise early when appropriate.
Monitor for sensory deficits and manage accordingly e.g. using hearing aids.
Keep the family involved and informed. Provide tools of care such as how to orientate and reassure the patient.

MEDICINE TREATMENT

For agitated and acutely disturbed patient:

- Olanzapine, oral dispersible tablet or IM, 2.5 to 5 mg.
  - This can be repeated in 30 to 60 minutes, if required and then 6 hourly to a maximum dose of 20 mg within 24 hours.
  - Monitor vital signs and beware of oversedation, neuroleptic malignant syndrome, and acute dystonia.

In hyperactive delirium or severe agitation or where there is no response or resistance to olanzapine:

ADD

- Lorazepam, oral, 0.5 to 1 mg 2 to 4 hourly as required.
  - Tablets may be crushed and administered sublingually. *LoE:IIIb*[xxi]

OR *LoE:IVb*[xxii]

Patients unable to swallow:

- Midazolam, SC/IV, 0.5 to 5 mg immediately. *LoE:IVb*[xxiii]
  - Titrate up slowly.
  - Lower doses are indicated for patients with liver dysfunction.

24.2.3 DEPRESSION

F32.0-3/F32.8-.9/F33.0-3/F33.8-9/F34.1 + (Z51.5)

DESCRIPTION

Depression is characterized by persistent feelings of extreme sadness and low mood associated with loss of interest in activities and inability to experience pleasure. There are often associated biological features of significant changes in appetite and weight, disturbed sleep, fatigue and poor concentration.

Diagnosis of major depression in a terminally ill patient often relies more on the psychological or cognitive symptoms (worthlessness, hopelessness, excessive guilt and suicidal ideation) than the physical/somatic signs (weight loss and sleep disturbance) described in depression in patients who are not terminally ill. The key indicators of depression in the terminally ill are persistent feelings of hopelessness and worthlessness and/or suicidal ideation.

Demoralisation is a phenomenon where hope and meaning is lost and where patients wish to hasten their death because they cannot foresee any future pleasure.

GENERAL MEASURES

Exclude physical reversible causes e.g. hypothyroidism, hyperthyroidism, or hypercalcaemia.

MEDICINE TREATMENT

- SSRI e.g.:
- Fluoxetine, oral. *LoE:IIb*[xxiv]
  - Initiate at 20 mg every alternate day for 2 weeks.
  - Increase to 20 mg daily after 2 to 4 weeks.
  - Delay dosage increase if increased agitation/panicked feelings occur.
  - Note: Fluoxetine is contraindicated if eGFR <10 mL/min.

LoE:IIb[xxv]

OR

- Citalopram, oral.
  - Initiate at 10 mg daily for 2 weeks.
  - Then increase to 20 mg daily.

LoE:IVb[xxvi]

OR

<u>If sedation is required:</u>

- Amitriptyline, oral, at bedtime.
  - Start with 25 mg, increase by 25 mg/day at 3-to 4-day intervals.
  - Dose range: 75 to 150 mg daily.

Note: Effect of SSRIs are only apparent after 2 to 3 weeks of treatment, so they should be reserved for patients where end-of-life is not imminent.

24.2.4 FATIGUE

R53 + (Z51.5)

DESCRIPTION

Fatigue is defined as a subjective feeling of tiredness, weakness or lack of energy. The pathophysiology is not fully understood but will be multifactorial in most palliative care patients, including disease- and treatment-related causes. Fatigue may be severe, distressing and persistent, regardless of adequate amounts of sleep and rest.

GENERAL MEASURES

Treat underlying causes such as anaemia, depression, and infections.
Encourage aerobic exercises, where appropriate.
Ensure that the multidisciplinary team assists with activity pacing, assisted devices where indicated, and diet.

MEDICINE TREATMENT

Note: Because of limited evidence, consideration of steroids in palliative care should be restricted to use in the terminally ill with fatigue and a specific short-term treatment goal.
Fatigue can also protect patients at the end of life from physical and emotional distress.

- Corticosteroids (intermediate-acting) e.g.:
- Prednisone, oral, 0.5 mg/kg (e.g.:15 to 30 mg) daily, for 1 week.

LoE:IIb[xxvii]

24.3 PAIN

See chapter 25: Pain.

24.3.1 CHRONIC CANCER PAIN

See Section 25.1.2: Analgesia for chronic cancer pain.

24.3.2 NEUROPATHIC PAIN

See Section 25.1.4: Neuropathic pain.

24.4 RESPIRATORY CONDITIONS

For Coronavirus Disease-19. See PHC Infections and related conditions Section 10.19.1: COVID-19: CORONAVIRUS DISEASE-19.

24.4.1 DYSPNOEA

R06.0+ (Z51.5)

DESCRIPTION

Dyspnoea is the subjective unpleasant sensation of being unable to breathe adequately (breathlessness). Dyspnoea is a complex multidimensional symptom with physical, psychological, and emotional dimensions, especially anxiety. The intensity of dyspnoea is generally not related to the oxygen saturation.

Look for reversible causes, e.g. infection, pulmonary embolism, pleural effusion, bronchospasm and anxiety

The aim should always be to address the cause. However, in end stage disease symptomatic treatment is indicated.

GENERAL MEASURES

Ideally, include a physiotherapist and occupational therapist for pulmonary rehabilitation and to teach patients pursed lip breathing, pacing of activities, relaxation techniques, and positioning.

The use of a fan may reduce the sensation of dyspnoea.

Treat the underlying cause (e.g. antibiotics for underlying respiratory infection) wherever possible.

MEDICINE TREATMENT

- Morphine syrup, oral.
  - Starting dose: 2.5 to 5 mg, 4 hourly as required, titrating up slowly.
  - In renal failure: start at 1 to 2 mg and observe patient closely before titrating up as required.

<u>Dyspnoea associated with hypoxaemia</u>

- Oxygen.

24.4.2 RESPIRATORY SECRETIONS

R06.8 + (Z51.5)

DESCRIPTION

Excessive respiratory tract secretions (also referred to as death rattle), is used to describe a rattling noise produced by accumulated secretions in the airway which oscillate in time with inspiration and expiration. Generally, respiratory secretions occur in patients who are extremely weak and close to death.

GENERAL MEASURES

Change position of the patient.

Explain to caregivers and relatives that the patient is not distressed by the secretion. Patients are not conscious that they are unable to clear secretions. Minimal oropharyngeal suctioning is required.

MEDICINE TREATMENT

- Hyoscine butylbromide, SC/IM, 20 mg.
  - Increase dose to effect to maximum of 120 mg.

LoE:IVb[xxviii]

24.5 SEDATION IN PALLIATIVE CARE

Z51.5

Sedation in palliative care has unique objectives, and tolerance for some adverse effects may be greater than in other situations. There is also an emphasis on avoiding parenteral medication. Palliative sedation should be undertaken by clinicians experienced in the process and the advice of an expert should be sought where necessary. Sedation should only be started after discussion with, and with the consent of, the patient and/or family (when the patient is unable to consent).

The aim of sedation in palliative care is to ameliorate refractory suffering and not to hasten death.
Palliative care medication addresses symptoms such as pain, dyspnoea, nausea and depression. Managing many of these symptoms involves the use of medications which may have sedative properties. Palliative sedation involves the additional use of medication where sedation is the primary objective and is appropriate only after standard care has proven unsuccessful.

GENERAL MEASURES

Pain must always be the first symptom to be excluded.
Always look for reversible causes of symptoms prior to prescribing sedation such as dehydration, hypoxia, concurrent synergistic sedative medicines, hypercalcaemia, renal failure, or infection.
Caution should be exercised and palliative care prescription examined for possible drug-drug interactions, prior to commencing sedation (or escalating doses of sedative medicines).
Dose escalation may be considered only if there is evidence of inadequate sedation.

MEDICINE TREATMENT

Dosing in frail, elderly patients should be titrated to effect.

- Lorazepam, oral, 0.5 mg 4 hourly.
  - Tablets may be crushed and administered sublingually.

OR *LoE:IVb*[xxix]

<u>If hyper active delirium or severe agitation</u>

- Olanzapine 2.5 to 5 mg orodispersible tablet or IM.
  - Repeat after 30 to 60 minutes if needed. *LoE:IVb*[xxx]

Note: Repeated doses may result in excessive sedation

Patient unable to take oral medication or terminal sedation required:

- Midazolam, SC/IV:
  - Initial dose: 1 to 5 mg as needed.
  - Titrate to effect.

LoE:IIb[xxxi]

24.6 MALODOROUS FUNGATING WOUNDS/TUMOURS

DESCRIPTION

Non-healing fungating tumours that are often secondarily infected and smelly causing social ostracization and distress to the patient and family. Examples include exophytic retinoblastoma, infected bedsores, rhabdomyosarcoma, osteosarcoma or Kaposi's sarcoma.

GENERAL AND SUPPORTIVE MEASURES

» Supportive counselling.
» Set realistic goals: may not include wound healing but could include odour eradication.
» Regular wound cleaning and dressing changes.
» Adequate ventilation.
» Disguise smell by placing a bowl of vanilla essence in the room, burn incense or place kitty litter under the bed to absorb smell.
» Air-fresheners and perfumes do not work.
» Change bedding and clothing regularly.

MEDICINE TREATMENT

- Provide good procedural pain management (see Chapter 25: Pain) and use distraction/relaxation techniques before and during dressing changes.
- Irrigate wounds with warmed normal saline. Debride gently with gloved hand not sharp instruments.
- Consider formal surgical debridement in patient where end-of-life is not imminent.
- Topical metronidazole:
  - Irrigation and cleaning of wound: 2 L saline combined with 13 crushed metronidazole 400 mg tablets (2 L 0.9% sodium chloride: 5200 mg metronidazole). Discard any remaining solution after each treatment, utilising appropriate medical waste management principles.
  - Metronidazole tablet topical: Metronidazole tablet 400 mg per 35 cm^2 area twice daily to ameliorate malodor.

LoE:IIIb[xxxii]

- Activated charcoal dressings also help to absorb odours.

- For wound pain consider using topical anaesthetics such as lidocaine/prilocaine.

LoE:IIIb[xxxiii]

24.7 END OF LIFE CARE

Z51.5

DESCRIPTION

Patients can be defined as being terminal when there is irreversible decline in functional status prior to death. It is essential during this time to ensure the ethical management of the dying phase and to minimise distress for the patient, family, and fellow health care professionals by using a biopsychosocial and spiritual approach.

Signs of dying:

» The patient may gradually spend more time sleeping during the day and at times will be difficult to rouse.
» There may be decreased need for food and drink.
» The patient may become increasingly confused about time, place and identity of friends and family.
» Arms and legs may become cool to the touch and the undersides of the body may become darker in colour.
» Loss of control of bowel and bladder may occur.
» Urine output may decrease.
» Saliva and mucus may collect at the back of the throat as the swallowing and cough reflexes diminish. This sometimes causes a noise known as the “death rattle”.
» Vision and hearing may decrease.
» Breathing patterns may become irregular, with longer intervals between breaths.

GENERAL MEASURES

Communication is at the centre of care. The following aspects should be addressed:

» Honest, direct, compassionate and culturally sensitive information about the prognosis.
» Evaluation of the patient and family resources and needs, especially spiritual needs.
» Decision making on place of death as many patients want to go home.
» Education about patient care.
» Emergency contact details, especially if the patient wants to go home.
» Compassionate information about symptoms that might develop and how to manage them.
» Nutrition and hydration.

Discontinue all non-essential, futile procedures and medicines e.g. discontinue 4-hourly blood pressure measurements and vitamin tablets.
Ensure medicines are prescribed for symptom management and prescribe medicine when needed to pre-empt common symptoms during the terminal phase using the appropriate route of administration:

» Pain (see section above).
» Nausea and vomiting (see section above).
» Respiratory secretions (see section above).
» Agitation /restlessness/delirium (see section above).

Discuss feeding and hydration with the family. If the decision is to hydrate and/ feed, ensure gentle hydration and monitor oedema, especially in patients with hypoalbuminaemia. Hydration does not improve quality of life, survival, or symptom burden at the end of life, and should not be given as routine management. Rather offer sips of water if the patient is able to swallow.

References:

[i] Palliative Care: SA Supportive and Palliative Care Indicators Tool (SPICTTM-SA). Available: file:///C:/Users/27798/Downloads/Version-2-SPICT-SA-Dec-2020%20(3).pdf.

[ii] Corticosteroids, oral/IV (anorexia/cachexia): National Department of Health: Affordable Medicines, EDP-Primary Health Care. Medicine Review: Betamethasone/dexamethasone for management of anorexia in adult palliative care patients, 29 July 2017. http://www.health.gov.za/

Corticosteroids, oral/IV (anorexia/cachexia): Miller S, McNutt L, McCann MA, McCorry N. Use of corticosteroids for anorexia in palliative medicine: a systematic review. J Palliat Med. 2014 Apr;17(4):482-5. https://www.ncbi.nlm.nih.gov/pubmed/24702642

Corticosteroids, oral/IV (anorexia/cachexia): Back I., Watson M., Lucas C., Hoy A. and Armstrong P. 2012. Anorexia, cachexia and asthenia. Palliative Care Guidelines Plus [Internet]. [Accessed 23 November 2017]. Available: http://book.pallcare.info/index.php?p=pdf&op_target=print&id=339&media=pdf&pdffmt=1&dq=1

[iii] Sennosides A and B, oral: South African Medicines Formulary, 14th Edition. Division of Clinical Pharmacology. University of Cape Town, 2022. Sennosides A and B, oral: Librach SL, Bouvette M, De Angelis C, Farley J, Oneschuk D, Pereira JL, Syme A; Canadian Consensus Development Group for Constipation in Patients with Advanced Progressive Illness. Consensus recommendations for the management of constipation in patients with advanced, progressive illness. J Pain Symptom Manage. 2010 Nov;40(5):761-73. https://www.ncbi.nlm.nih.gov/pubmed/21075273

[iv] Lactulose, oral: Librach SL, Bouvette M, De Angelis C, Farley J, Oneschuk D, Pereira JL, Syme A; Canadian Consensus Development Group for Constipation in Patients with Advanced Progressive Illness. Consensus recommendations for the management of constipation in patients with advanced, progressive illness. J Pain Symptom Manage. 2010 Nov;40(5):761-73. https://www.ncbi.nlm.nih.gov/pubmed/21075273

Sennosides A and B, oral AND lactulose: Candy B, Jones L, Larkin PJ, Vickerstaff V, Tookman A, Stone P. Laxatives for the management of constipation in people receiving palliative care. Cochrane Database Syst Rev. 2015 May 13;(5):CD003448. https://www.ncbi.nlm.nih.gov/pubmed/25967924

[v] Bisacodyl suppository: Canadian Agency for Drugs and Technologies in Health (CADTH). Rapid response report - Routine Bowel Care for Patients in Long-Term or Palliative Care: Guidelines; 2015 Dec 7. [Internet]. Canadian [cited 2017 October 30]. Available from: https://www.cadth.ca/sites/default/files/pdf/htis/dec-2015/RB0940%20Bowel%20Care%20in%20LTC%20Final.pdf

Bisacodyl suppository: Larkin PJ ,Sykes NP, Centeno C, Ellershaw JE, Elsner F, Eugene B, Gootjes JRG, Naba M, Noguera IA, Ripamonti C, Zucco F, Zuurmond WWA .The management of constipation in palliative care: clinical practice recommendations Palliative Medicine. Vol 22, Issue 7, pp.796 – 807. http://dx.doi.org/10.1177%2F0269216308096908

Bisacodyl suppository: National Department of Health: Affordable Medicines, EDP-Primary Health Care. Medicine Review: Bisacodyl suppository in palliative care, 29 August 2017. http://www.health.gov.za/

[vi] Palliative Medicine: Cherny N, Fallon M, Kaasa S. Oxford Textbook of Palliative Medicine. Oxford: OUP Oxford; 2015. Available from: http://UOCT.eblib.com/patron/FullRecord.aspx?p=2012658.

[vii] Metoclopramide, oral nausea and vomiting): South African Medicines Formulary, 14th Edition. Division of Clinical Pharmacology. University of Cape Town, 2022.

[viii] Haloperidol, oral/parenteral: Digges M, Hussein A, Wilcock A, Crawford GB, Boland JW, Agar MR, Sinnarajah A, Currow DC, Johnson MJ. Pharmacovigilance in Hospice/Palliative Care: Net Effect of Haloperidol for Nausea or Vomiting. J Palliat Med. 2018 Jan;21(1):37-43. https://www.ncbi.nlm.nih.gov/pubmed/28772094

Haloperidol, oral/parenteral: Doyle D, Woodruff R. The IAHPC Manual of Palliative Care. 3rd ed. IAHPC Press, 2013. Available from: https://hospicecare.com/what-we-do/publications/manual-of-palliative-care/ [Accessed August 2019]

[ix] Olanzapine, oral (anti-emetic): Saudemont, G., Prod'Homme, C., Da Silva, A. et al. The use of olanzapine as an antiemetic in palliative medicine: a systematic review of the literature. BMC Palliat Care 19, 56 (2020). https://doi.org/10.1186/s12904-020-00559-4

Olanzapine, oral (anti-emetic): Palliative Medicine: Cherny N, Fallon M, Kaasa S. Oxford Textbook of Palliative Medicine. Oxford: OUP Oxford; 2015. Available from: http://UOCT.eblib.com/patron/FullRecord.aspx?p=2012658.

Olanzapine (Adults: Nausea and vomiting in palliative care): National Department of Health: Affordable Medicines, EDP- Adult. Medicine Review: Olanzapine injection, orodispersible. Adult palliative care patients with nausea and vomiting not responding to metoclopramide, November 2022. http://www.health.gov.za/

[x] Orphenadrine, oral (parkinsonism side-effects): South African Medicines Formulary, 14th Edition. Division of Clinical Pharmacology. University of Cape Town, 2022. .

[xi] Promethazine, IM/IV: Wiffen, P. Palliative Care Formulay 5th edition, 2014. http://www.palliativedrugs.com/

[xii] Benzodiazepines: Salt S, Mulvaney CA, Preston NJ. Drug therapy for symptoms associated with anxiety in adult palliative care patients. Cochrane Database Syst Rev. 2017 May 18;5:CD004596. https://www.ncbi.nlm.nih.gov/pubmed/28521070

[xiii] Diazepam, oral (anxiety): South African Medicines Formulary, 14th Edition. Division of Clinical Pharmacology. University of Cape Town, 2022..

[xiv] Lorazepam, oral (anxiety): BCGuidelines.ca. Palliative Care for the Patient with Incurable Cancer or Advanced Disease - Part 2: Pain and Symptom Management, 22 February 2017 [Internet] [Accessed 23 November 2017]. Available at: https://www2.gov.bc.ca/gov/content/health/practitioner-professional-resources/bc-guidelines/palliative-pain-management

[xv] Lorazepam, oral formulation administered sublingually (anxiety): Greenblatt DJ, Divoll M, Harmatz JS, Shader RI. Pharmacokinetic comparison of sublingual lorazepam with intravenous, intramuscular, and oral lorazepam. J Pharm Sci. 1982 Feb;71(2):248-52. https://www.ncbi.nlm.nih.gov/pubmed/6121043

[xvi] Diazepam, parenteral (liver impairment): South African Medicines Formulary, 14th Edition. Division of Clinical Pharmacology. University of Cape Town, 2022. .
[xvii] Benzodiazepines: South African Medicines Formulary, 14th Edition. Division of Clinical Pharmacology. University of Cape Town, 2022. .
[xviii]SSRIs, oral (anxiety): Salt S, Mulvaney CA, Preston NJ. Drug therapy for symptoms associated with anxiety in adult palliative care patients. Cochrane Database Syst Rev. 2017 May 18;5:CD004596. https://www.ncbi.nlm.nih.gov/pubmed/28521070
[xix] Fluoxetine, oral (anxiety): Baldwin D, Woods R, Lawson R, Taylor D. Efficacy of drug treatments for generalised anxiety disorder: systematic review and meta-analysis. BMJ. 2011;342:d1199. https://www.ncbi.nlm.nih.gov/pubmed/21398351
Fluoxetine, oral (anxiety): South African Medicines Formulary, 14th Edition. Division of Clinical Pharmacology. University of Cape Town, 2022..
[xx] Citalopram, oral (anxiety): South African Medicines Formulary, 14th Edition. Division of Clinical Pharmacology. University of Cape Town, 2022..
[xxi]Lorazepam (): Hui D, Frisbee-Hume S, Wilson A, Dibaj SS, Nguyen T, De La Cruz M, Walker P, Zhukovsky DS, Delgado-Guay M, Vidal M, Epner D, Reddy A, Tanco K, Williams J, Hall S, Liu D, Hess K, Amin S, Breitbart W, Bruera E. Effect of Lorazepam With Haloperidol vs Haloperidol Alone on Agitated Delirium in Patients With Advanced Cancer Receiving Palliative Care: A Randomized Clinical Trial. JAMA. 2017 Sep 19;318(11):1047-1056. https://www.ncbi.nlm.nih.gov/pubmed/28975307
Lorazepam dose: South African Medicines Formulary, 14th Edition. Division of Clinical Pharmacology. University of Cape Town, 2022.
[xxii] Lorazepam, oral formulation administered sublingually (anxiety): Greenblatt DJ, Divoll M, Harmatz JS, Shader RI. Pharmacokinetic comparison of sublingual lorazepam with intravenous, intramuscular, and oral lorazepam. J Pharm Sci. 1982 Feb;71(2):248-52. https://www.ncbi.nlm.nih.gov/pubmed/6121043
[xxiii]Midazolam, IV/SC (delirium): NHS Scotland. Scottish Palliative Care Guidelines – Delirium, 15 April 2014. [Internet] [Accessed 23 November 2017] Available at: http://www.palliativecareguidelines.scot.nhs.uk/guidelines/symptom-control/Delirium.aspx
Midazolam, IV/SC (delirium): Bush SH, Tierney S, Lawlor PG. Clinical Assessment and Management of Delirium in the Palliative Care Setting. Drugs. 2017 Oct;77(15):1623-1643. https://www.ncbi.nlm.nih.gov/pubmed/28864877
[xxiv]SSRIs, oral (anxiety): Salt S, Mulvaney CA, Preston NJ. Drug therapy for symptoms associated with anxiety in adult palliative care patients. Cochrane Database Syst Rev. 2017 May 18;5:CD004596. https://www.ncbi.nlm.nih.gov/pubmed/28521070
[xxv] Fluoxetine, oral (anxiety): Baldwin D, Woods R, Lawson R, Taylor D. Efficacy of drug treatments for generalised anxiety disorder: systematic review and meta-analysis. BMJ. 2011;342:d1199. https://www.ncbi.nlm.nih.gov/pubmed/21398351
Fluoxetine, oral (anxiety): South African Medicines Formulary, 14th Edition. Division of Clinical Pharmacology. University of Cape Town, 2022..
[xxvi]Citalopram, oral (anxiety): South African Medicines Formulary, 14th Edition. Division of Clinical Pharmacology. University of Cape Town, 2022..
[xxvii]Corticosteroids (fatigue): Mücke M; Mochamat, Cuhls H, Peuckmann-Post V, Minton O, Stone P, Radbruch L. Pharmacological treatments for fatigue associated with palliative care. Cochrane Database Syst Rev. 2015 May 30;(5):CD006788. https://www.ncbi.nlm.nih.gov/pubmed/26026155
Corticosteroids (fatigue): National Department of Health: Affordable Medicines, EDP-Primary Health Care. Medicine Review: Betamethasone/dexamethasone for management of fatigue in adult palliative care patients, 29 July 2017. http://www.health.gov.za/
Corticosteroids (fatigue): Radbruch L, Strasser F, Elsner F, Gonçalves JF, Løge J, Kaasa S, Nauck F, Stone P; Research Steering Committee of the European Association for Palliative Care (EAPC). Fatigue in palliative care patients -- an EAPC approach. Palliat Med. 2008 Jan;22(1):13-32. https://www.ncbi.nlm.nih.gov/pubmed/18216074
[xxviii] Hyoscine butylbromide, SC/IM, (respiratory secretions): National Department of Health: Affordable Medicines, EDP-Adult Hospital Level. Medicine Review: Hyoscine butylbromide for management of respiratory secretions in adult palliative care patients, December 2017. http://www.health.gov.za/
Hyoscine butylbromide, SC/IM, (respiratory secretions): NICE guideline: Care of dying adults in the last days of life, 16 December 2015. Available at: https://www.nice.org.uk/guidance/ng31
Hyoscine butylbromide, SC/IM, (respiratory secretions): NHS Lanarkshire Palliative Care Guidelines, March 2012. [Internet] [Accessed January 2018] Available at: http://www.nhslanarkshire.org.uk/Services/PalliativeCare/Documents/NHS%20Lanarkshire%20Palliative%20Care%20Guidelines.pdf
Hyoscine butylbromide, SC/IM, (respiratory secretions): Waitemata District Health Board Palliative Care Guidelines: Hyoscine N-Butylbromide, subcutaneous, April 2016. [Internet] [Accessed January 2018] Available at: http://www.waitematadhb.govt.nz/health-professionals/medicines/palliative-care-guidelines/
[xxix] Lorazepam, oral formulation administered sublingually (anxiety): Greenblatt DJ, Divoll M, Harmatz JS, Shader RI. Pharmacokinetic comparison of sublingual lorazepam with intravenous, intramuscular, and oral lorazepam. J Pharm Sci. 1982 Feb;71(2):248-52. https://www.ncbi.nlm.nih.gov/pubmed/6121043
[xxx] Olanzapine, oral: South African Medicines Formulary. 14th Edition. Division of Clinical Pharmacology. University of Cape Town. 2022.
[xxxi]Midazolam IV/SC: Schildmann EK, Schildmann J, Kiesewetter I. Medication and monitoring in palliative sedation therapy: a systematic review and quality assessment of published guidelines. J Pain Symptom Manage. 2015 Apr;49(4):734-46. https://www.ncbi.nlm.nih.gov/pubmed/25242022

Midazolam, SC/IV: Cherny NI, Radbruch L; Board of the European Association for Palliative Care. European Association for Palliative Care (EAPC) recommended framework for the use of sedation in palliative care. Palliat Med. 2009 Oct;23(7):581-93. https://www.ncbi.nlm.nih.gov/pubmed/19858355
[xxxii]Metronidazole (Wound Odor): De Castro DLV, de Gouveia Santos VLC. Controlling wound odor with metronidazole: a systematic review. Rev Esc Enferm USP. 2015, 49 (5):851-856.
Metronidazole (Malodorous fungating tumours): Ashford R, Plant G, Maher J, Teare L. Double-blind trial of metronidazole in malodorous ulcerating tumours. Lancet. 1984;1(8388):1232-3.
Metronidazole (Malodorous fungating tumours): Bower M, Stein R, Evans TR, Hedley A, Coombes RC. A doble-blind study of the efficacy of metronidazole gel in the treatment of malodorous fungating tumours. Eur J Cancer. 1992;28A(4-5):888-9.
[xxxiii](Activated Charcoal Dressings): Kerihuel JC. Effect of activated charcoal dressings on healing outcomes of chronic wounds. J Wound Care. 2010 May;19(5):208, 210-2, 214-5. doi: 10.12968/jowc.2010.19.5.48047. PMID: 20505594.

CHAPTER 25
PAIN

25.1 PAIN, CHRONIC
R52.1/R52.2/R52.9

DESCRIPTION
An unpleasant sensory and emotional experience associated with, or resembling that associated with, actual or potential tissue damage. The relationship between pain (a subjective experience) and tissue damage (which may be assessed directly by others) is moderated by socio-cultural context as well as the nervous system. Acute pain is defined as pain present for less than 4 weeks and usually occurs in response to tissue damage. Chronic pain is pain present for more than 3 months.

LoE:IVb[i]

The goals of pain management include pain reduction and improved function, sleep, and well-being. Family members play an important part in the patient's treatment and should be included where possible.

Measure care outcomes by evaluating pain severity, quality of life, and functionality, e.g. Pain, Enjoyment and General Activity (PEG) scale, https://health.gov/hcq/trainings/pathways/assets/pdfs/PEG_scale.pdf.

25.1.1 ANALGESIA FOR CHRONIC NON-CANCER PAIN

Assessment of chronic non-cancer pain
A biopsychosocial assessment is necessary to inform effective pain management.

Ascertain the aetiology and perpetuating factors and manage accordingly. Note that there may be overlap between different aetiologies, and condition-specific pain management may be required:

» Nociceptive pain, e.g. see Sections 13.1: Arthritis, rheumatoid (RA); Section 13.3: osteoarthritis; Section 13.4: gout; Section 13.5: Seronegative spondylarthritis; chronic post-surgical or injury pain; visceral pain, e.g. Section 1.1.7: Pancreatitis, chronic; Section 24.3.1: Chronic cancer pain and Section 5.4: Endometriosis.
» Neuropathic pain (see Section 25.1.4).
» Fibromyalgia and irritable bowel syndrome – see Primary Health Care (PHC) Standard Treatment Guidelines (STG) and Essential Medicines List (EML), Section 2.12: Irritable bowel syndrome (IBS).
» Mental illness, e.g. mood disorders (depression and bipolar disorder), anxiety, post-traumatic stress disorder (see Chapter 15: Mental health conditions), somatic symptoms, and related disorders.

» Substance use disorders, including over the counter analgesics, opioids, benzodiazepines, and alcohol.

Ascertain the patient's beliefs about their pain and hopes of care. Common issues to address are:

» Patients' perception of pain and the idealised nature of reality, e.g. that life must be pain-free.
» That pain means exercise and physical activity must be avoided.
» Catastrophic thinking regarding the pain.
» A need to be unwell to be cared for by others.
» Fear of work and responsibility, for various reasons.
» Stigma, with denial of mental illness or interpersonal conflict.

Social stressors, trauma, interpersonal conflict or violence may predispose to and perpetuate chronic pain.

GENERAL AND SUPPORTIVE MEASURES

Patients with chronic pain should be treated with a biopsychosocial approach, ideally using a multidisciplinary team, according to findings of a comprehensive assessment. Note that those with greater subjective pain complaints may also be at higher risk of an opioid use disorder.

LoE:IIIb[ii]

» Validate the pain experienced and manage with empathy.
» Explore and manage exacerbating factors for pain. See Section 25.1: Chronic pain.
» Educate regarding the cause of pain, prognosis (including that pain may not be fully relieved), and realistic expectations regarding pain reduction.
» Establish goals of care with the patient and select a measure of effectiveness e.g. Pain, Enjoyment and General Activity (PEG) scale, https://health.gov/hcq/trainings/pathways/assets/pdfs/PEG_scale.pdf
» Treat the underlying physical cause of pain. Refer for specialist care (e.g. rheumatologist, orthopaedic surgeon) where necessary.
» Treat underlying or comorbid mental illness.
» Manage substance use disorder, refer to SANCA/ rehabilitative services.
» Encourage physical activity; refer to Physiotherapy and Occupational Therapy (OT).
» Address self-esteem, motivation, daily function, and social skills; refer to OT.
» Address social stressors and interpersonal conflicts; refer to social worker, counselling services, psychologist, social welfare organisations, NGOs (e.g. FAMSA, https://www.famsawc.org.za; or POWA, https://www.powa.co.za, if domestic violence is reported).

LoE:IIIb[iii]

MEDICINE TREATMENT

Paracetamol, ibuprofen and tramadol may be used alone or in combination according to the severity of pain.

Mild/moderate pain:

- Paracetamol, oral, 500 mg to 1 g, 4 to 6 hourly as required (to a maximum of 4 g in 24 hours).
  - Maximum dose: 15 mg/kg/dose.

- NSAID, e.g.: *LoE:IIb*[iv]
- Ibuprofen, oral, 400 mg 8 hourly with meals.
  - May be used in combination with paracetamol and/or opioids.

CAUTION - NSAIDs

» Avoid long-term use of NSAIDs (e.g. ibuprofen) as they are associated with increased risk of arterial thrombosis, renal impairment and GI bleeding.
» Concomitant use of more than one NSAID has no additional clinical benefit and only increases toxicity.
» All NSAIDs are associated with increased risks of gastrointestinal bleeding, renal dysfunction, and cardiovascular events (stroke and myocardial infarction).
» Use NSAIDs judiciously at the lowest effective dose and for the shortest duration.
» Do not use NSAIDs in pregnancy or while breastfeeding.

In high-risk patients: i.e. patients >65 years of age, or with a history of peptic ulcer disease, or on concomitant warfarin, aspirin or corticosteroids:

ADD *LoE:IIb*[v]

- PPI, e.g.:
- Lansoprazole, oral, 30 mg daily.

Moderate pain unresponsive to simple analgesia:

- Tramadol, oral, 50–100 mg, 6 hourly; may be increased to a maximum of 400 mg daily.
  - Warn patient of adverse effects and risk of addiction. Advise not to operate machinery/drive initially and after dosage increases.
  - Evaluate response to treatment using a pain rating scale at 2 weeks and every 4 weeks afterwards: **taper and stop tramadol if not reducing pain.** See PHC STG & EML, Section 20.1: Pain control for rating scales.
  - In patients with uncontrolled pain, the dose can be increased to a maximum of 100 mg 6 hourly.
  - Improved effect when given with paracetamol. *LoE:IVb*[vi]

CAUTION – TRAMADOL

» Tramadol causes respiratory depression and may be fatal in overdose.
» Avoid concurrent prescribing of opioid pain medication, benzodiazepines or other respiratory depressants.
» After a period of no treatment, re-initiate at 50 mg. Treat overdose as in Section 19.5.3. Opioid poisoning.
» Avoid use in those at high risk of opioid addiction (a personal or family history of any substance use disorder, comorbid mental illness, high levels of subjective pain and younger people). The Opioid Risk Tool (ORT) is a brief, self-report screening tool used to assess risk for opioid abuse among adults prescribed opioids for treatment of chronic pain. https://nida.nih.gov/sites/default/files/opioidrisktool.pdf

LoE:IVb[vii]

» Tramadol inhibits reuptake of noradrenaline and serotonin – increases risk of seizures, of serotonin syndrome, and mania or hypomania. Use with caution in high-risk patient groups (e.g. epilepsy, severe head injury, if taking antidepressants, bipolar disorder). Educate the patient, optimise treatment of primary condition, avoid polypharmacy, and monitor closely.
» Other adverse effects include constipation, dry mouth, drowsiness, and confusion.

LoE:IVb[viii]

OR

- Morphine solution (Mist morphine), oral.
  - Starting dose: 5–10 mg (maximum 0.2 mg/kg) 4 hourly.
  - Elderly or frail patients: 2.5–5 mg oral (maximum 0.1 mg/kg) 4 hourly.
  - Increase total daily dose by 30% every 24 hours if pain control is inadequate.
  - Increase the dosing interval in patients with renal or liver impairment.

LoE:Ivb[ix]

When stable on morphine solution, the morphine solution can be changed to an equivalent dose of long-acting, slow-release morphine:

- Morphine, slow-release, oral, 12 hourly.
  - Available in tablets of 10 mg, 30 mg, and 60 mg.
  - Duration of action: 12 hours.
  - Dose according to previous morphine solution requirements, e.g. a patient whose pain is controlled by 6 doses of 10 mg morphine solution per 24 hours (i.e. 60 mg morphine per day) can be converted to receive slow-release morphine tablets, 30 mg 12 hourly, oral.
  - Maximum dose for non-cancer pain is usually 60 mg 12 hourly.

Note:

» When morphine is used for chronic non-cancer pain, discuss potential

side-effects with the patient, the maximum dose of opioids that will be prescribed, and anticipated duration of treatment. Address all fears and concerns with the patient to alleviate fear. Provide support and education for caregivers and family.

» Patients with breakthrough pain should be treated appropriately. See PHC STG & EML, Section 20.5: Breakthrough Pain.
» Avoid in patients with history of alcohol or other drug addiction, where possible.

25.1.2 ANALGESIA FOR CHRONIC CANCER PAIN

DESCRIPTION

The term “cancer pain” also includes pain due to “palliative care needs/ serious illness”.

GENERAL MEASURES

Follow the same steps as provided in Section 25.1.1: Analgesia for chronic non-cancer pain, with the following exceptions:

Morphine:

» There is no maximum dose of morphine – Titrate as needed.
» Concerns regarding addiction/dependency should not compromise adequate pain control with opioids when used to treat “palliative care needs/serious illness”.
» For patients on slow-release morphine, it is advisable to still prescribe morphine solution for breakthrough pain or for painful procedures.
» Breakthrough pain is a transient exacerbation of pain which occurs either spontaneously or in relation to a specific trigger despite relatively stable and adequately controlled background pain. It may or may not be at the same location as the background/controlled pain.
» Treat breakthrough pain by giving an extra dose of immediate-release morphine equal to the regular 4-hour dose (i.e. one sixth of the total daily dose).
» The next regular dose of morphine must still be given at the prescribed time, and not be delayed because of the additional dose.

LoE:IVb[x]

The regular 4-hourly dosage should be titrated upward against the effect on pain in the following way:

» Add up the amount of “breakthrough morphine” needed in 24 hours.
» Divide this amount by 6 (the number of 4 hourly doses in 24 hours).
» The next day increase maintenance dose by that amount.

Example:

» Patient receives 10 mg morphine every four hours.

» The patient has 3 episodes of breakthrough pain over 24 hours and is given an additional 10 mg during each episode:
  – Total breakthrough pain dosage: 3 x 10 mg = 30 mg.
  – Dose to add to maintenance dose the following day: 30 mg ÷ 6 = 5 mg.
» The day following the breakthrough pain, the regular 4 hourly dose of 10 mg will be increased by 5 mg, i.e. 10 mg + 5 mg = 15 mg.
» The new morphine dose will be 15 mg 4 hourly.

Note:
» Opioid–induced hyperalgesia is defined as increasing pain sensitivity in patients chronically exposed to opioids without any new causes for pain. Increasing doses of morphine paradoxically result in increased pain, often with features of neuropathic pain such as hyperalgesia or allodynia (consult with a pain clinician/specialist).

Bisphosphonates may be considered for metastatic bone pain – refer to the Tertiary and Quaternary EML (specialist management/consultation).

25.1.3 TREATMENT OF ADVERSE EFFECTS OF CHRONIC OPIOID USE

Y45.0

MEDICINE TREATMENT

Constipation: (K59.0)
Patients on chronic opioids should routinely be prescribed a laxative.
- Sennosides A and B, oral, 13.5 mg, 1–2 tablets at night.
  - Contraindicated in patients with potentially obstructive lesions.

LoE:IVb[xi]

In patients with potentially obstructive lesions:
- Lactulose, oral, 10–20 mL 12–24 hourly.

LoE:IVb[xii]

Nausea and vomiting: (R11)
- Metoclopramide, oral/IM/slow IV, 10 mg 8 hourly (see Section 12.6.5.2: treatment of PONV).

OR
- Promethazine, oral, 25 mg 8 hourly.

LoE:IVb

OR
- Ondansetron, oral, 8 mg 12 hourly.

25.1.4 NEUROPATHIC PAIN

G62.9

DESCRIPTION

Pain caused by a lesion or disease of the somatosensory nervous system.

LoE:IVb[xiii]

Different patterns are noted, i.e. polyneuropathy, mononeuritis multiplex, and mononeuropathy, each of which may be caused by axonal degeneration or demyelination or a combination of the above. Clinical features may be predominantly of a sensory, sensorimotor, or motor nature.

Important causes of a predominantly sensory neuropathy include:
» alcohol;
» diabetes;
» HIV infection;
» Vitamin deficiency: thiamine, vitamin B12 (although the latter more commonly presents as subacute combined degeneration of the cord);
» medicines (e.g. isoniazid, stavudine, metronidazole, amiodarone, certain chemotherapeutic agents).

Important causes of a predominantly motor neuropathy include:
» Acute Inflammatory Demyelinating Polyradiculoneuropathy (AIDP – also known as Guillain-Barrè syndrome),
» Chronic Inflammatory Demyelinating Polyradiculoneuropathy (CIDP),
» Acute porphyrias

GENERAL MEASURES

» If there is a history of rapid progression, particularly in patients with features suggestive of AIDP, (e.g. rapid progression with stabilisation within 4 weeks) admit the patient and monitor vital capacity carefully with spirometry, as intubation and ventilatory support may be required.
» Manage the cause where possible.
» Specialised nursing care and dedicated physiotherapy may be indicated. If not managed appropriately, chronic cases may develop contractures, weakness affecting gait, and chronic bedsores, and they may become wheel chair-bound. Encourage activity, with referral to OT and physiotherapy.
» Address psychosocial stressors and enhance perceived social support, and refer to social worker as required.
» Treat comorbid mental illness (see Chapter 15: Mental health conditions).
» Assess outcome of treatment with objective measures of function, e.g. Pain, Enjoyment and General Activity (PEG) scale: https://health.gov/hcq/trainings/pathways/assets/pdfs/PEG_scale.pdf

MEDICINE TREATMENT

Most cases respond to management of the underlying disease process or removal of the aetiological agent.

In addition to the analgesics for chronic nociceptive pain (see Section 25.1.1: Analgesia for chronic non-cancer pain), anti-neuropathic pain medicines to stabilise affected sensory nerves can be used.

- Amitriptyline, oral, 10 mg, two hours before usual sleep time.
  - Titrate up to 75 mg (to a maximum of 150 mg) at night if needed. LoE:IIb[xiv]
  - In the elderly: 10–25 mg daily, increasing gradually up to 50–100 mg daily, if required and tolerated. A single bedtime dose is optimal for most patients. LoE:Ivb[xv]
  - Use regularly as it takes 2–6 weeks for maximal effect. LoE:IIIb[xvi]

Post-herpetic neuralgia: (G53.0)
Initiate treatment with adjuvant amitriptyline therapy early. LoE:IIIb[xvii]

<u>If no response after 2-4 weeks to amitriptyline:</u>

ADD
- Carbamazepine, oral, 100mg 12 hourly for 2 weeks.
  - If response is inadequate, increase the dose every 2 weeks to a maximum dose of 600 mg 12 hourly.
  - Monitor for possible drug interactions in patients on ART. LoE:Iib[xviii]

<u>If amitriptyline is contraindicated:</u>

REPLACE WITH
- Carbamazepine, oral, 100mg 12 hourly for 2 weeks.
  - If response is inadequate, increase the dose every 2 weeks to a maximum dose of 600 mg 12 hourly.
  - Monitor for possible drug interactions in patients on ART. LoE:Iib[xix]

Note: Aciclovir is not beneficial in treating post-herpes zoster neuropathy.

Isoniazid–induced polyneuropathy: (G62.9 + Y41.1)
- Pyridoxine, oral 75 mg daily for 3 weeks.
  - Follow with 25 to 50 mg daily.

Trigeminal neuralgia (G50.0)
Sudden, usually unilateral, severe, brief, stabbing, recurrent episodes of pain in the distribution of one or more branches of the trigeminal nerve.

- Carbamazepine, oral 100 mg 12 hourly, initial dose.
  - Increase dose slowly. Doses of up to 1 200 mg daily may be required.
  - After exacerbation, reduce to maintenance dose of 400 to 800 mg daily. LoE:Ivb[xx]

REFERRAL

» Neuropathic pain unresponsive to these medicines, refer patient to an experienced pain clinician.

25.2 ANALGESIA FOR ACUTE NON-SURGICAL PAIN

25.2.1 MEDICAL CONDITIONS ASSOCIATED WITH SEVERE PAIN

R52.0/R52.1/R52.2/R52.9

DESCRIPTION

There are numerous medical conditions associated with severe acute or chronic pain e.g. myocardial infarction, renal colic, sickle-cell crisis and intra-articular haemorrhage due to haemophilia.

GENERAL MEASURES

» The analgesic treatment for these conditions is as for patients with acute post-operative pain (see Section 12.4.2: Postoperative pain in the recovery room).

» Patients should be monitored for respiratory and cardiovascular depression when IV opioids are administered.
Patients already on opioids for chronic pain, who experience an acutely painful event, may be opioid tolerant and require higher IV opioid doses to control their pain.

25.2.2 ACUTE PAIN DUE TO GASTROINTESTINAL COLIC

R10.0-4

MEDICINE TREATMENT

- Hyoscine butylbromide, IV/oral, 10 mg 8 hourly.

References:

[i] Definitions: International Association for the Study of Pain. IASP Announces Revised Definition of Pain. 2020. https://www.iasp-pain.org/resources/terminology//

[ii] Management of chronic pain: Scascighini L, Toma V, Dober-Spielmann S, Sprott H. Multidisciplinary treatment for chronic pain: a systematic review of interventions and outcomes. Rheumatology (Oxford). 2008 May;47(5):670-8. doi: 10.1093/rheumatology/ken021. Epub 2008 Mar 27. PMID: 18375406

[iii] Management of chronic non-cancer pain: Dowell D, Haegerich TM, Chou R. CDC Guideline for Prescribing Opioids for Chronic Pain--United States, 2016. JAMA. 2016 Apr 19;315(15):1624-45. https://www.ncbi.nlm.nih.gov/pubmed/26977696

Management of chronic non-cancer pain: Ballantyne JC, Kalso E, Stannard C. WHO analgesic ladder: a good concept gone astray. BMJ. 2016 Jan 6;352:i20. https://www.ncbi.nlm.nih.gov/pubmed/26739664

Management of chronic non-cancer pain: The Royal College of Anaesthetists. Opioid Aware Resource, 2019. [Accessed August 2019]. https://www.rcoa.ac.uk/faculty-of-pain-medicine/opioids-aware

Management of chronic non-cancer pain: Ortho-Mcneil Pharmaceutical, Inc. The U.S. Food and Drug Administration approved drug label for tramadol tablets, 2008. https://www.accessdata.fda.gov/drugsatfda_docs/label/2009/020281s032s033lbl.pdf

[iv] NSAIDs as a therapeutic class (diclofenac, naproxen, ibuprofen): Affordable Medicines, EDP-Adult Hospital level. NSAIDs – comparative review of efficacy and safety, 15 January2018. http://www.health.gov.za

NSAIDs as a therapeutic class (diclofenac, naproxen, ibuprofen): Van Walsem A, Pandhi S, Nixon RM, Guyot P, Karabis A, Moore RA. Relative benefit-risk comparing diclofenac to other traditional non-steroidal anti-inflammatory drugs and cyclooxygenase-2 inhibitors in patients with osteoarthritis or rheumatoid arthritis: a network meta-analysis. Arthritis Research & Therapy 2015;17:66. https://www.ncbi.nlm.nih.gov/pubmed/25879879

NSAIDs as a therapeutic class (diclofenac, naproxen, ibuprofen): Nissen SE, Yeomans ND, Solomon DH, Lüscher TF, et al. Cardiovascular Safety of Celecoxib, Naproxen, or Ibuprofen for Arthritis. N Engl J Med 2016;375:2519-29. https://www.ncbi.nlm.nih.gov/pubmed/28379793

NSAIDs as a therapeutic class (diclofenac, naproxen, ibuprofen): Coxib and traditional NSAID Trialists' (CNT) Collaboration. Vascular and upper gastrointestinal effects of non-steroidal anti-inflammatory drugs: meta-analyses of individual participant data from randomised trials. Lancet 2013; 382: 769–79. https://www.ncbi.nlm.nih.gov/pubmed/23726390

NSAIDs as a therapeutic class (diclofenac, naproxen, ibuprofen): Trelle S, Reichenbach S, Wandel S, Hildebrand P, Tschannen B, et al. Cardiovascular safety of non-steroidal anti-inflammatory drugs: network meta-analysis. BMJ 2011;342:c7086. https://www.ncbi.nlm.nih.gov/pubmed/21224324

NSAIDs as a therapeutic class (diclofenac, naproxen, ibuprofen): Ong CKS, Lirk P, Tan Ch, Seymour RA. An evidence-based update on nonsteroidal anti-inflammatory drugs. Clinical Medicine and Research 2007; 5(1):19-34. https://www.ncbi.nlm.nih.gov/pubmed/17456832

NSAIDs as a therapeutic class (diclofenac, naproxen, ibuprofen): Stam WB, Jansen JP, Taylor SD. Efficacy of etoricoxib, lumiracoxib, non-selective NSAIDs, and acetaminophen in osteoarthritis: a mixed treatment comparison. The Open Rheumatology Journal 2012; 6:6-20. https://www.ncbi.nlm.nih.gov/pubmed/22582102

NSAIDs as a therapeutic class (diclofenac, naproxen, ibuprofen): Bello AE, Holt RJ. Cardiovascular risk with non-steroidal anti-inflammatory drugs: clinical implications. Drug Saf. 2014 Nov;37(11):897-902. https://www.ncbi.nlm.nih.gov/pubmed/25079141

NSAIDs as a therapeutic class (diclofenac, naproxen, ibuprofen): South African Medicines Formulary, 14th Edition. Division of Clinical Pharmacology. University of Cape Town, 2022..

[v] Lansoprazole, oral (high risk patients on chronic NSAID therapy): McQuaidKR ,Laine L . Systemic review and meta-analysis of adverse events of low-dose aspirin and clopidogrel in randomized controlled trials. Am J Med 2006;119:624–38. http://www.ncbi.nlm.nih.gov/pubmed/16887404

Lansoprazole, oral (high risk patients on chronic NSAID therapy): Serrano P, Lanas A, Arroyo MT, Ferreira IJ. Risk of upper gastrointestinal bleeding in patients taking low-dose aspirin for the prevention of cardiovascular diseases. Aliment PharmacolTher. 2002 Nov;16(11):1945-53. http://www.ncbi.nlm.nih.gov/pubmed/12390104

Lansoprazole, oral (high risk patients on chronic NSAID therapy): Lanza FL, Chan FK, Quigley EM; Practice Parameters Committee of the American College of Gastroenterology. Guidelines for prevention of NSAID-related ulcer complications. Am J Gastroenterol. 2009 Mar;104(3):728-38. http://www.ncbi.nlm.nih.gov/pubmed/19240698

[vi] Tramadol, oral: Dowell D, Haegerich TM, Chou R. CDC Guideline for Prescribing Opioids for Chronic Pain–United States, 2016. JAMA. 2016 Apr 19;315(15):1624-45. https://www.ncbi.nlm.nih.gov/pubmed/26977696

Tramadol, oral: Ortho-Mcneil Pharmaceutical, Inc. The U.S. Food and Drug Administration approved drug label for tramadol tablets, 2008. https://www.accessdata.fda.gov/drugsatfda_docs/label/2009/020281s032s033lbl.pdf

Tramadol, oral: The Royal College of Anaesthetists. Opioid Aware Resource, 2019. [Accessed August 2019]. https://www.rcoa.ac.uk/faculty-of-pain-medicine/opioids-aware

[vii] Opioid Risk Tool: Questionnaire developed by Lynn R. Webster, MD to assess risk of opioid addiction. Webster LR, Webster R. Predicting aberrant behaviors in Opioid-treated patients: preliminary validation of the Opioid risk too. Pain Med. 2005; 6 (6) : 432https://nida.nih.gov/sites/default/files/opioidrisktool.pdf

[viii] Tramadol – caution: Dowell D, Haegerich TM, Chou R. CDC Guideline for Prescribing Opioids for Chronic Pain–United States, 2016. JAMA. 2016 Apr 19;315(15):1624-45. https://www.ncbi.nlm.nih.gov/pubmed/26977696

Tramadol – caution: The Royal College of Anaesthetists. Opioid Aware Resource, 2019. [Accessed August 2019]. https://www.rcoa.ac.uk/faculty-of-pain-medicine/opioids-aware

Tramadol – caution: Kaye AD, Jones MR, Kaye AM, Ripoll JG, Galan V, Beakley BD, Calixto F, Bolden JL, Urman RD, Manchikanti L. Prescription Opioid Abuse in Chronic Pain: An Updated Review of Opioid Abuse

Predictors and Strategies to Curb Opioid Abuse: Part 1. Pain Physician. 2017 Feb;20(2S):S93-S109. https://www.ncbi.nlm.nih.gov/pubmed/28226333

Tramadol– caution: Beakley BD, Kaye AM, Kaye AD. Tramadol, Pharmacology, Side Effects, and Serotonin Syndrome: A Review. Pain Physician. 2015 Jul-Aug;18(4):395-400. https://www.ncbi.nlm.nih.gov/pubmed/26218943

Tramadol – caution: Sharma V. Tramadol-Induced Hypomania and Serotonin Syndrome. Prim Care Companion CNS Disord. 2016 Dec 15;18(6). https://www.ncbi.nlm.nih.gov/pubmed/28002658

Tramadol – caution: Hassamal S, Miotto K, Dale W, Danovitch I. Tramadol: Understanding the Risk of Serotonin Syndrome and Seizures. Am J Med. 2018 Nov;131(11):1382.e1-1382.e6. https://www.ncbi.nlm.nih.gov/pubmed/29752906

[ix] Morphine syrup (Dosage Increase): Charlesworth, S. (Ed.). (2020). Palliative Care Formulary (7th ed.). Pharmaceutical Press

Morphine syrup (Dosage Increase): Carver AC and Foley KM (2001) Symptom assessment and management. Neurologic Clinics. 19: 921–947

[x] Breakthrough Pain: Charlesworth, S. (Ed.). (2020). Palliative Care Formulary (7th ed.). Pharmaceutical Press

[xi] Sennosides A and B, oral: South African Medicines Formulary, 14th Edition. Division of Clinical Pharmacology. University of Cape Town, 2022.

[xii] Lactulose, oral: South African Medicines Formulary, 14th Edition. Division of Clinical Pharmacology. University of Cape Town, 2022.

[xiii] Definition (Neuropathic Pain): International Association for the Study of Pain. 2020.https://www.iasp-pain.org/resources/terminology/

[xiv] Amitriptyline, oral: Moore RA, Derry S, Aldington D, Cole P, Wiffen PJ. Amitriptyline for neuropathic pain in adults. Cochrane Database Syst Rev. 2015 Jul 6;7:CD008242. http://www.ncbi.nlm.nih.gov/pubmed/26146793

Amitriptyline, oral: Chetty S, Baalbergen E, Bhigjee AI, Kamerman P, Ouma J, Raath R, Raff M, Salduker S; South African Expert Panel. Clinical practice guidelines for management of neuropathic pain: expert panel recommendations for South Africa. S Afr Med J. 2012 Mar 8;102(5):312-25. http://www.ncbi.nlm.nih.gov/pubmed/22554341

Amitriptyline: Charlesworth, S. (Ed.). (2020). Palliative Care Formulary (7th ed.). Pharmaceutical Press.

Amitriptyline: Mahmoud AMS, Ragab SG, Boules ML, Botros JM. Comparison between Two Low Doses of Amitriptyline in the Management of Chronic Neck Pain: A Randomized, Double-Blind, Comparative Study. Pain Res Manag. 2021 Jan 19;2021:8810178. doi: 10.1155/2021/8810178. PMID: 33532013; PMCID: PMC7837778.

[xv] Amitriptyline, oral (dosing in the elderly): South African Medicines Formulary, 14th Edition. Division of Clinical Pharmacology. University of Cape Town, 2022..

[xvi] Amitriptyline, oral (time to maximal effect): Onghena P, Van Houdenhove B. Antidepressant-induced analgesia in chronic non-malignant pain: a meta-analysis of 39 placebo-controlled studies. Pain. 1992 May;49(2):205-19. https://www.ncbi.nlm.nih.gov/pubmed/1535121

[xvii] Amitriptyline, oral: Bowsher D. The effects of pre-emptive treatment of postherpetic neuralgia with amitriptyline: a randomized, double-blind, placebo-controlled trial. J Pain Symptom Manage. 1997 Jun;13(6):327-31.http://www.ncbi.nlm.nih.gov/pubmed/9204652

[xviii] Carbamazepine, oral (neuropathy): Wiffen PJ, Derry S, Moore RA, Kalso EA. Carbamazepine for chronic neuropathic pain and fibromyalgia in adults. Cochrane Database Syst Rev. 2014 Apr 10;(4):CD005451. https://www.ncbi.nlm.nih.gov/pubmed/24719027

Carbamazepine, oral (neuropathy): South African Medicines Formulary, 14th Edition. Division of Clinical Pharmacology. University of Cape Town, 2022.

[xix] Carbamazepine, oral (neuropathy): Wiffen PJ, Derry S, Moore RA, Kalso EA. Carbamazepine for chronic neuropathic pain and fibromyalgia in adults. Cochrane Database Syst Rev. 2014 Apr 10;(4):CD005451. https://www.ncbi.nlm.nih.gov/pubmed/24719027

Carbamazepine, oral (neuropathy): South African Medicines Formulary, 14th Edition. Division of Clinical Pharmacology. University of Cape Town, 2022.

[xx] Carbamazepine, oral (trigeminal neuralgia): The National Institute for Health and Care Excellence. Neuropathic pain – pharmacological management, February 2017. NICE clinical guideline 173. http://guidance.nice.org.uk/CG173

The list of antimicrobial medicines, below, excludes antiretroviral medicines.
It is important to refer to the text of the standard treatment guidelines for detailed information of specific medicines for specific indications (i.e. duration of therapy, if used in combination with other antibiotics, prescriber level, etc.).

ACICLOVIR

4.5: Atopic eczema/dermatitis, eczema herpeticum (if patient is unable to swallow due to odynophagia):

- **Aciclovir, IV, 5 mg/kg/dose 8 hourly for 7 days.**

9.12: Varicella (chickenpox), complicated, 9.13: Zoster (Shingles) (For zoster with secondary dissemination or neurological involvement/complicated eye involvement (i.e. complicated herpes zoster ophthalmicus e.g. acute retinal necrosis (ARN), optic neuropathy or orbitopathy), 14.8.2: Viral meningoencephalitis - Herpes simplex encephalitis, 18.4: Herpes zoster opthalmicus:

- **Aciclovir, IV, 10 mg/kg 8 hourly.**

9.12: Varicella (chickenpox), complicated, 9.13: Zoster (Shingles), 18.4: Herpes zoster ophthalmicus:

- **Aciclovir, oral, 800 mg five times a day or 4 hourly while awake.**

4.5: Atopic eczema/dermatitis, eczema herpeticum; 18.5.1: Keratitis, herpes simplex;

- **Aciclovir, oral, 400 mg 8 hourly for 7 days or five times a day for 10-14 days or 12 hourly.**

AMIKACIN A

- *2.2: Febrile neutropenia, 9.1.3: Hospital-acquired pneumonia (HAP) and ventilator-associated pneumonia (VAP), 9.1.4: Urinary tract infections, catheter associated::***Amikacin, IV, 15 mg/kg daily**.

*10.1.1: Management of selected antiretroviral adverse drug reactions, Hepatitis in patients on ART and anti-tuberculosis therapy***:**

- **Amikacin, IV/IM, 15 mg/kg daily**.

23.10.3 Sepsis In ICU: Antimicrobial therapy:

- **Amikacin.**

AMOXICILLIN A

3.7: Rheumatic heart disease - All patients with confirmed rheumatic fever and persistent rheumatic valvular disease:

- **Amoxicillin, oral, 250mg daily.**

6.12: Preterm Labour (PTL) and preterm prelabour rupture of membranes (PPROM):

- **Amoxicillin, oral, 500 mg 8 hourly for 5 days**.

1.1.8: Peptic ulcer, H. pylori eradication:

- **Amoxicillin, oral, 1 g 12 hourly for 14 days.**

3.7: Rheumatic heart disease - acute rheumatic fever (for eradication of streptococci in throat):

- **Amoxicillin, oral, 1 000 mg (1 gram) 12 hourly for 10 days.**

3.5: Endocarditis, infective, prophylaxis:

- **Amoxicillin, oral, 2 g one hour before the procedure.**

16.6: Pneumonia, community acquired (uncomplicated), 17.4: Otitis media, acute:

- **Amoxicillin, oral, 1 g 8 hourly.**

AMOXICILLIN/CLAVULANIC ACID A

1.1.2: Diverticulosis, uncomplicated, 1.2.5: Liver abscess, pyogenic, 1.2.7: Cholecystitis, acute and cholangitis, acute, 1.3.8: Bacterial peritonitis, 4.7: Leg ulcers, complicated, 5.3: Pelvic inflammatory disease (PID) Stage II-IV, 5.8.4: Septic miscarriage, 6.16: Postpartum fever, 6.19.2: Urinary tract infection (UTI) in pregnancy: Pyelonephritis, acute, 8.7.3: Diabetic foot ulcers, 16.3: Bronchiectasis, In patients otherwise stable and before culture results and more severely ill patients may require hospitalisation and initiation of parenteral antibiotic therapy, 16.4: Chronic obstructive pulmonary disease (COPD), 16.5: Lung abscess, 16.6: Pneumonia, community acquired, 16.7: Pneumonia, aspiration, 16.8: Empyema - If not a complication of pneumonia, 17.1: Epiglottis, 17.4: Otitis media, acute (patients not responding to amoxicillin), 17.8: Abscess, peritonsillar, 19.2: Snakebites: secondary infection:

- **Amoxicillin/clavulanic acid 875/125 mg, oral, 12 hourly.**

1.1.2: Diverticulosis - uncomplicated, unable to tolerate oral therapy, 1.2.5: Liver abscess, pyogenic, 1.2.7: Cholecystitis, acute and cholangitis, acute - If unable to tolerate oral therapy, 1.1.6: Pancreatitis acute: for infected necrosis of the pancreas, 1.3.8: Bacterial peritonitis, 5.8.4: Septic miscarriage, 6.16: Postpartum fever, 8.7.3: Diabetic foot ulcers: severe infection, 16.5: Lung abscess, 16.7: Pneumonia, aspiration, 16.8: Empyema - If not a complication of pneumonia, 17.8: Abscess, peritonsillar:

- **Amoxicillin/clavulanic acid, IV, 1.2 g 8 hourly.**

23.10.3: Sepsis In ICU: Antimicrobial therapy:

- **Amoxicillin/clavulanic acid, IV, loading dose - 1.2 g over 30 minutes.**

23.10.3: Sepsis In ICU: Antimicrobial therapy:

- **Amoxicillin/clavulanic acid, IV, maintenance dose - 1.2 g infusion given over 4 hours, 6 hourly dosing intervals.**

23.10.3: Sepsis In ICU: Antimicrobial therapy:

- **Amoxicillin/clavulanic acid**

AMPHOTERICIN B

9.1.1: Intravascular catheter infections, short-term central venous catheter infection: candidaemia - Empiric antifungal therapy:

- **Amphotericin B, IV, 0.7 mg/kg daily.**

2.2: Febrile neutropenia,10.2.4.3: Cryptococcal meningitis, 14.8.1.2.2: Cryptococcal meningitis, HIV-uninfected, 23.10.3 Sepsis in ICU: Antimicrobial therapy:

- **Amphotericin B, IV, 1 mg/kg daily.**

10.2.4.2: Cryptococcal meningitis - If liposomal amphotericin B and flucytosine are available:

Liposomal amphotericin B, slow IV infusion over 2 hours, 10 mg/kg in dextrose 5%, single dose.

10.2.4.2: Cryptococcal meningitis - If liposomal amphotericin B is not available,

- **Amphotericin B deoxycholate, slow IV infusion, 1 mg/kg daily in dextrose 5% over 4 hours for 7 days**

10.2.4.2: Cryptococcal meningitis - If flucytosine is not available:

- **Amphotericin B deoxycholate, slow IV infusion, 1 mg/kg daily**
- **in dextrose 5% over 4 hours for 14 days**

AMPICILLIN A

6.11.1 Preterm labour (PTL) and preterm prelabour rupture of membranes (PPROM), 16.6: Pneumonia, community acquired - without severe features co-morbid patients <65 years of age:

- **Ampicillin, IV, 1 g 6 hourly.**

3.5: Endocarditis, infective, prophylaxis, if patient cannot take oral medicines:

- **Ampicillin, IV/IM, 2 g one hour before the procedure.**

3.5: Endocarditis, infective - empiric therapy - native valve, 3.5: Endocarditis, infective - directed therapy (native valve) - streptococcal - fully susceptible to penicillin, 3.5: Endocarditis, infective - directed therapy (native valve) - streptococcal - moderately susceptible, 3.5: Endocarditis, infective - enterococcal, susceptible to penicillin:

- **Ampicillin, IV, 2 g 6 hourly.**

14.8.1: Meningitis: Listeria monocytogenes meningitis:

- **Ampicillin, IV, 3 g 6 hourly for 21 days.**

23.10.3: Sepsis In ICU: Antimicrobial Therapy

- **Ampicillin.**

AZITHROMYCIN W

3.7: Rheumatic heart disease, acute rheumatic fever and all patients with confirmed rheumatic fever and persistent rheumatic valvular disease, severe penicillin allergy:

- **Azithromycin, oral, 250 mg daily.**

11: Surgical Antibiotic prophylaxis:

- **Azithromycin, 500 mg, IV, as a single dose.**

16.6: Pneumonia, community acquired (severe pneumonia):

- **Azithromycin, 500 mg, slow IV (over not less than 60 minutes) daily for 3 days.**

1.1.8: Peptic ulcer, severe penicillin allergy, 3.7: Rheumatic heart disease, acute rheumatic fever - severe penicillin allergy, 4.2: Cellulitis and erysipelas – severe penicillin allergy, 4.3: Impetigo – severe penicillin allergy, 9.10: Tick bite fever, in pregnancy, 16.4: Chronic obstructive pulmonary disease (COPD) - severe penicillin allergy, 17.1: Epiglottitis - severe penicillin allergy - to amoxicillin/clavulanic acid, oral, 17.4: Otitis media, acute - severe penicillin allergy:

- **Azithromycin, oral, 500 mg daily for 3 days.**

10.2.8: Mycobacteriosis - disseminated non-tuberculous

- **Azithromycin, oral, 500 mg daily.**

*5.3: Pelvic Inflammatory Disease (PID) - stage I, 5.3: Pelvic Inflammatory Disease (PID), stage II-IV: (for severe penicillin allergy), 5.10: Sexual Assault (STI prophylaxis), 6.11.1: Preterm labour (PTL) and preterm prelabour rupture of membranes (PPROM) - Antibiotic therapy and severe penicillin allergy 7.3.4: Prostatitis (acute bacterial prostatitis), 13.2: Arthritis, septic and osteomyelitis, acute, 13.5.1: Arthritis, reactive: 10.5.2: Non occupational post exposure prophylaxis, sexual assault (STI prophylaxis**),** 16.3: Bronchiectasis - severe penicillin allergy, 18.1.4 Conjunctivitis, bacterial (gonococcal):*

- **Azithromycin, oral, 1 g as a single dose.**

5.3: Pelvic Inflammatory Disease (PID) - stage I, severe penicillin allergy:

- **Azithromycin, oral, 2 g as a single dose.**

11: Surgical Antibiotic prophylaxis, 23.10.3 Sepsis In ICU: Antimicrobial therapy:

- **Azithromycin.**

BENZATHINE BENZYLPENICILLIN A

3.7: Rheumatic heart disease, p*revention of recurrent rheumatic fever - All patients with confirmed rheumatic fever and persistent rheumatic valvular disease (treat lifelong):*

- **Benzathine benzylpenicillin (depot formulation), IM, 1.2 MU every 3–4 weeks.**

3.7: Rheumatic heart disease, acute rheumatic fever - For eradication of streptococci in throat:

- **Benzathine benzylpenicillin (depot formulation), IM, 1.2 MU as a single dose.**

6.7: Syphilis, asymptomatic well baby:

- **Benzathine benzylpenicillin (depot formulation), IM, 50 000 units/kg as a single dose into the antero-lateral thigh.**

6.7: Syphilis, mother - For late latent syphilis or syphilis of unknown duration:

- **Benzathine benzylpenicillin (depot formulation), IM, 2.4 million units diluted in 6 mL 1% lidocaine without adrenaline (epinephrine), weekly for 3 doses.**

6.7: Syphilis, mother - For early syphilis:

- **Benzathine benzylpenicillin (depot formulation), IM, 2.4 million units diluted in 6 mL 1% lidocaine without adrenaline (epinephrine), immediately as a single dose.**

BENZYLPENICILLIN A

6.7: Syphilis, symptomatic baby:

- **Benzylpenicillin (Penicillin G), IV, 50 000 units/kg, 12 hourly for 10 days.**

3.5: Endocarditis, infective – Directed therapy (native valve) streptococcal, **Fully susceptible to penicillin** *, 3.5: Endocarditis, infective – Directed therapy (native valve) streptococcal, moderately susceptible:*

- **Benzylpenicillin (penicillin G), IV, 5 MU 6 hourly for 4 weeks.**

3.5: Endocarditis, infective – Directed therapy (native valve) Enterococcal, **Susceptible to penicillin** *:*

- **Benzylpenicillin (penicillin G), IV, 5 MU 6 hourly for 4-6 weeks. 6 weeks of therapy may be required in cases with a history of >3 months, or when the regimen is combined with ceftriaxone.**

14.8.1: Meningitis (meningococcal meningitis – for confirmed meningococcal disease only), 14.8.1: Meningitis (pneumococcal meningitis - If sensitive to penicillin):

- **Benzylpenicillin (penicillin G), IV, 20–24 MU daily in 4–6 divided doses for one week.**

14.8.3: Meningovascular syphilis (Neurosyphilis):

- **Benzylpenicillin (penicillin G), IV, 20 MU daily in 4–6 divided doses for 10 days.**

CEFALEXIN A

4.2: Cellulitis and erysipelas, 9.12 Varicella (chickenpox), complicated:

- **Cefalexin, oral, 500 mg 6 hourly for 5 days.**

CEFAZOLIN A

11: Cardiac surgery, 11: Endoscopic gastrointestinal procedures, 11: Gastrointestinal surgery, 11: General surgery, 11: Neurosurgery, 11: Obstetrics/ gynaecology, 11: Orthopaedic surgery, 11: Otorhinolaryngology/ head and neck surgery, 11: Plastic and reconstructive surgery, 11: Thoracic surgery, 11: Urology, 11: Vascular surgery:

- **Cefazolin, IV, 1-3 g as a single dose.**

4.2: Cellulitis and erysipelas, 4.4: Furuncles and abscesses, 9.1.2: Surgical wound infections:

- **Cefazolin, IV, 1 g 8 hourly.**

3.5: Endocarditis, infective - Directed therapy (native valve) staphylococcal - cloxacillin-susceptible (methicillin-susceptible)

- **Cefazolin, IV, 2 g, 8 hourly for 4 weeks.**

3.5: Endocarditis, infective – empiric therapy for native valve, 13.2: Arthritis, septic and osteomyelitis, acute:

- **Cefazolin, IV, 2 g 8 hourly.**

CEFEPIME W

2.2: Febrile neutropenia, 9.1.3: Hospital-acquired pneumonia (HAP) and ventilator-associated pneumonia (VAP):

- **Cefepime, IV, 2 g 12 hourly.**

CEFTAZIDIME W

18.2: Endophthalmitis, bacterial (endogenous endophthalmitis and post-surgical endophthalmitis):

- **Ceftazidime, intravitreal, 2.25 mg.**

CEFTAZIDIME-AVIBACTAM R

23.10.3: Sepsis in ICU: Antimicrobial therapy

- **Ceftazidime-avibactam, 2.5 g, IV, 8 hourly (Microbiologist or Infectious Disease specialist initiated).**

CEFTRIAXONE W

5.3: Pelvic Inflammatory Disease (PID), stage I, 5.10: Sexual assault - STI prophylaxis, 7.3.4: Prostatitis, acute bacterial prostatitis - if there are features of associated urethritis (STI regimen), 10.5.2: Non occupational post exposure prophylaxis, sexual assault STI Prophylaxis, 13.5.1: Arthritis, reactive - If urethritis is present, treatment may prevent further episodes of arthritis, 18.1.4 *Conjunctivitis, Bacterial (Gonococcal):*

- **Ceftriaxone, IM, 250 mg as a single dose.**

1.3.2: Dysentery (Acute inflammatory diarrhoea), 1.3.8: Bacterial peritonitis - spontaneous, 2.2: Febrile neutropenia, 5.3: Pelvic Inflammatory Disease (PID), stage II-IV, 6.19.2: Pyelonephritis, acute, 7.3.2: Urinary tract infection (UTI), acute pyelonephritis: impaired renal function, 13.2: Arthritis, septic and osteomyelitis, acute - for gonococcal arthritis, 17.1: Epiglottitis:

- **Ceftriaxone, IV, 1 g, daily.**

3.5: Endocarditis, infective enterococcal, susceptible to penicillin, 9.11: Typhoid fever (enteric fever), 14.8.1: Meningitis – Antibiotic therapy - Empiric therapy for bacterial meningitis, until sensitivity results are available, 14.8.1: Meningitis - pneumococcal meningitis - If resistant to penicillin, 14.8.1: Meningitis - haemophilus influenzae, 14.8.4: Brain abscess, 14.8.5: Antimicrobial use in patients with head injuries, penetrating brain injuries, 17.3: Sinusitis, bacterial, complicated, 17.6: Mastoiditis:

- **Ceftriaxone, IV, 2 g 12 hourly.**

16.3: Bronchiectasis, 16.6: Pneumonia, community acquired, without features of severe pneumonia in patients >65 years of age or co-morbidity (e.g. COPD, HIV, cardiac failure, diabetes), 16.6: Pneumonia, community acquired, severe pneumonia, 18.2: Endophthalmitis, bacterial (endogenous endophthalmitis), 20.12.2.2: Septic shock, 9.1.2: Surgical wound infections: female uro-genital tract, open GIT surgery:

- **Ceftriaxone 2 g, IV, daily.**

23.10.3 Sepsis In ICU: Antimicrobial therapy:

- **Ceftriaxone.**

CHLORAMPHENICOL A

18.1.3: Conjunctivitis, bacterial (non-gonococcal), 18.10.1: Chemical burn:

- **Chloramphenicol 1%, ophthalmic ointment, applied 6 hourly.**

19.2.3: Snake venom in the eye:

- **Chloramphenicol 1%, ophthalmic ointment, applied 8 hourly.**

11: Ophthalmic surgery:

- **Chloramphenicol 0.5% ophthalmic drops, instil 1 drop 2–4 hourly for 24 hours prior to surgery.**

CIPROFLOXACIN W

17.5: Otitis media, chronic, suppurative:

- **Ciprofloxacin 3mg/mL ophthalmic drops, 3–4 drops instilled into the ear every 8 hours for 7 days after mopping.**

18.1.3: Conjunctivitis, bacterial (non-gonococcal), 18.5.2: Keratitis, suppurative - Empiric therapy until culture results become available:

- **Ciprofloxacin 0.3%, ophthalmic drops.**

14.8.1: Meningitis, nasopharyngeal carriage eradication, 14.8.1: Meningitis, prophylaxis of contacts:

- **Ciprofloxacin, oral, 500 mg immediately as a single dose.**

1.3.2: Dysentery (acute inflammatory diarrhoea), 1.3.8: Bacterial peritonitis - for spontaneous bacterial peritonitis, 5.3: Pelvic inflammatory disease (stage II-IV) – severe penicillin allergy, 5.8.4: Septic miscarriage, severe penicillin allergy de-escalation therapy, 7.3.2: Urinary tract infection (Complicated community acquired cystitis (non-pregnant women), 7.3.2: Urinary tract infection (UTI), acute pyelonephritis - If normal renal function 7.3.2: Urinary tract infection (UTI), acute pyelonephritis - If impaired renal function: de-escalation therapy, 7.3.4: Prostatitis - If there are no features of associated urethritis, 7.3.4: Prostatitis - Chronic/relapse/persistent infection 9.1.4: Urinary tract infections, catheter associated - If local resistance patterns show low level resistance to ciprofloxacin or culture shows sensitivity, 9.11: Typhoid fever (enteric fever), 9.11: Typhoid fever (enteric fever), chronic carriers, 9.11: Typhoid fever (enteric fever), following ceftriaxone IV, based on culture sensitivity results,10.2.7: Cystoisosporiasis, If allergic to cotrimoxazole:

- **Ciprofloxacin, oral, 500 mg 12 hourly.**

16.3: Bronchiectasis, pseudomonas infection confirmed on culture, 17.7.1: Otitis externa, necrotising. 18.2: Endophthalmitis, bacterial, if there is soft tissue involvement or as prophylaxis after a penetrating eye injury:

- **Ciprofloxacin, oral, 750 mg 12 hourly for 7 days.**

1.3.1: Cholera:

- **Ciprofloxacin, oral, 1g single dose.**

9.10: Tick bite fever, pregnant, if patient is unable to tolerate oral therapy:

- **Ciprofloxacin, IV, 400 mg 8 hourly.**

CLINDAMYCIN A

4.2: Cellulitis and erysipelas, severe penicillin allergy, 4.4: Furuncles and abscesses, severe penicillin allergy, 5.3: Pelvic Inflammatory Disease (PID), stage II-IV: severe penicillin allergy, 5.8.4: Septic miscarriage, severe penicillin allergy, 6.11.1: Preterm Labour (PTL) and Preterm prelabour rupture of membranes (PPROM) - Antibiotic therapy, severe penicillin allergy, 9.1.2: Surgical wound infections, severe penicillin allergy, 13.2: Arthritis, septic and osteomyelitis, acute: severe penicillin allergy, 17.8: Abscess, peritonsillar, severe penicillin allergy:

- **Clindamycin, IV, 600 mg 8 hourly.**

3.5: Endocarditis, infective, prophylaxis: severe penicillin allergy (if patient cannot take oral), 11: Surgical Antibiotic Prophylaxis:

- **Clindamycin, IV, 600 mg as a single dose.**

8.7.3: Diabetic foot ulcers, severe penicillin allergy:

- **Clindamycin, oral, 150-450 mg 8 hourly.**

4.2: Cellulitis and erysipelas: severe infection - severe penicillin allergy, 4.4: Furuncles and abscesses: severe penicillin allergy, 4.5: Atopic eczema/dermatitis: severe penicillin allergy, 5.3: Pelvic Inflammatory Disease (PID), stage II-IV: severe penicillin allergy, de-escalation therapy, 5.8.4: Septic miscarriage, severe penicillin allergy, de-escalation therapy, 6.11.1: Preterm Labour (PTL) and preterm prelabour rupture of membranes (PPROM) - Antibiotic therapy, severe penicillin allergy, 9.1.1: Intravascular catheter infections, erythema beyond catheter site, 9.1.2: Surgical wound infections, severe penicillin allergy, de-escalation therapy, 13.2: Arthritis, septic and osteomyelitis, acute: severe penicillin allergy, 17.8: Abscess, peritonsillar: severe penicillin allergy, 21.2.2: Extravasations:

- **Clindamycin, oral, 450 mg 8 hourly.**

3.5: Endocarditis, infective, prophylaxis, severe penicillin allergy:
Clindamycin, oral, 600 mg one hour before the procedure.

10.2.9: Pneumocystis pneumonia, cotrimoxazole intolerance, unsuccessful cotrimoxazole desensitisation and if primaquine is not available:

- **Clindamycin, oral, 600 mg 8 hourly for 21 days.**

23.10.3 Sepsis In ICU: Antimicrobial therapy

- **Clindamycin.**

CLOTRIMAZOLE

4.10: Fungal infections, yeast and dermatophytes (fungal infection of the skin) :

- **Clotrimazole 1%, topical, apply 8 hourly until clear of disease (i.e. for at least 2 weeks after the lesions have cleared).**

CLOXACILLIN A

3.5: Endocarditis, infective: Empiric therapy, native valve, 3.5: Endocarditis, infective directed therapy, native valve, staphylococcal, cloxacillin-susceptible (methicillin-susceptible):

- **Cloxacillin, IV, 3 g, 6 hourly.**

23.10.3 Sepsis In ICU: Antimicrobial therapy

- **Cloxacillin.**

COTRIMOXAZOLE (TRIMETHOPRIM/SULFAMETHOXAZOLE) A

7.3.3: Recurrent UTI, prophylaxis:

- **Cotrimoxazole 80/400 mg, oral, 1 tablet at night.**

10.2.2: Opportunistic infection prophylaxis, with cotrimoxazole, 10.2.7: Cystoisosporiasis, secondary prophylaxis, 10.2.9: Pneumocystis pneumonia, secondary prophylaxis:

- **Cotrimoxazole, oral, 160/800 daily.**

10.2.10: Cerebral toxoplasmosis, secondary prophylaxis:

- **Cotrimoxazole, oral, 320/1600 daily.**

10.2.7: Cystoisosporiasis:

- **Cotrimoxazole 320/1600 mg, oral, 12 hourly for 10 days.**

10.2.9: Pneumocystis pneumonia: <60kg:

- **Cotrimoxazole, oral, 240/1200 mg, oral, 6 hourly for 21 days.**

10.2.9: Pneumocystis pneumonia, ≥ 60kg:

- **Cotrimoxazole 320/1600 mg, oral, 6 hourly for 21 days.**

10.2.9: Pneumocystis pneumonia, if vomiting:

- **Cotrimoxazole, IV, 6 hourly for 21 days.**
  - < 60 kg 240/1200 mg.
  - ≥ 60 kg 320/1600 mg

10.2.10: Cerebral toxoplasmosis:

- **Cotrimoxazole 320/1600 mg, oral, 12 hourly for 28 days, followed by 160/800 mg 12 hourly for 3 months.**

10.2.9: Pneumocystis pneumonia:

- **Cotrimoxazole intolerance and desensitisation**

23.10.3 Sepsis In ICU: Antimicrobial Therapy

  - **Cotrimoxazole.**

DAPSONE

10.2.9: Pneumocystis pneumonia, if primaquine not available:

- **Dapsone, oral, 100 mg daily for 21 days.**

10.2.9: Pneumocystis pneumonia, secondary prophylaxis, cotrimoxazole intolerant:

- **Dapsone, oral, 100 mg daily.**

DOXYCYCLINE A

9.10: Tick bite fever: Non-pregnant - treatment duration: Treat for 7 days (if afebrile), or until at least 3 days after the fever has subsided.

- **Doxycycline, oral, 100 mg 12 hourly.**

9.10: Tick bite fever: If pregnant:

- **Doxycycline, oral, 100 mg 12 hourly for 2 days.**

9.3: Brucellosis:

- **Doxycycline, oral, 100 mg 12 hourly for 6 weeks.**

ECHINOCANDIN

9.1.1: Intravascular catheter infections (specialist motivation):

- **Echinocandins**

ERTAPENEM W

9.1.2: Surgical wound infections - severe penicillin allergy - (gram-negative organism):

- **Ertapenem, IV, 1 g daily.**

ETHAMBUTOL

16.11.1: Confirmed isoniazid monoresistant and contraindication to isoniazid:

- **Ethambutol, oral, 15 mg/kg daily. Treatment should be given for at least 6 months.**

10.2.8: Mycobacteriosis - disseminated non-tuberculous:

- **Ethambutol, oral, 15–20 mg/kg daily.**

10.1.1: Management of selected antiretroviral adverse drug reactions: Hepatitis in patients on ART and anti-tuberculosis therapy:

- **Ethambutol, oral, 800 - 1200 mg daily.**

FLUCLOXACILLIN A

13.2: Arthritis, septic and osteomyelitis, acute:

- **Flucloxacillin, oral, 1 g 6 hourly to complete the 4 weeks' treatment.**

4.2: Cellulitis and erysipelas, 4.3: Impetigo, 4.4: Furuncles and abscesses, 4.5: Atopic eczema/dermatitis (infected eczema), 9.1.2: Surgical wound Infections - Check Gram stain of exudate. If organism is gram negative, 9.12: Varicella (chickenpox), complicated – secondary infection, 9.13: Zoster (Shingles)-

secondary infection - if there is suspected associated bacterial cellulitis:

- **Flucloxacillin, oral, 500 mg 6 hourly.**

FLUCONAZOLE

4.10: Fungal infections, Systemic antifungal therapy, 4.10: Fungal infections, onychomycosis:

- **Fluconazole, oral, 200 mg weekly.**

10.2.3: Candidiasis of oesophagus/trachea/bronchi, 10.2.4.1: Cryptococcosis, CSF Crag Negative - maintenance phase, 10.2.4.2: Cryptococcal meningitis, maintenance phase, 14.8.1.2.2: Cryptococcal meningitis, HIV-uninfected-maintenance therapy:

- **Fluconazole, oral, 200 mg daily.**

10.2.3: Candidiasis of oesophagus/trachea/bronchi:

- **Fluconazole, IV/oral, 200 mg daily.**

9.1.1: Intravascular catheter infections, short-term central venous catheter infection candidaemia - follow up susceptibility, 14.8.1.2.2: Cryptococcal meningitis, HIV-uninfected:

- **Fluconazole, oral, 400 mg daily**

10.2.4.1: Cryptococcosis, CSF CRAG negative, consolidation phase, 10.2.4.2: Cryptococcal meningitis, consolidation phase, 14.8.1.2.2: Cryptococcal meningitis, HIV-uninfected:

- **Fluconazole, oral, 800 mg daily**

14.8.1.2.2: Cryptococcal meningitis, HIV-uninfected:

- **Fluconazole, oral, 400 mg daily**

10.2.4.1: Cryptococcosis, CSF CRAG negative - induction phase, 10.2.4.2: Cryptococcal meningitis, induction phase - If liposomal amphotericin B and flucytosine are available and if flucytosine is not available:

- **Fluconazole, oral, 1200 mg daily**

23.10.3 Sepsis In ICU: Antimicrobial therapy

- **Fluconazole, IV, loading dose: 800 mg daily then maintenance dose: 400 mg daily.**

FLUCYTOSINE

10.2.4.2: Cryptococcal meningitis – induction phase - If liposomal amphotericin B and flucytosine are available:

- **Flucytosine, oral, 25 mg/kg 6 hourly for 14 days.**

10.2.4.2: Cryptococcal meningitis If liposomal amphotericin B is not available:

- **Flucytosine, oral, 25 mg/kg 6 hourly for 7 days.**

FOSFOMYCIN W

6.19.1: Cystitis, 7.3.2: Urinary tract infection (UTI) - Uncomplicated community acquired cystitis and pregnant women:

- **Fosfomycin 3 g, oral, as a single dose.**

GANCICLOVIR

10.2.6: Cytomegalovirus (CMV) - Biopsy-proven GIT disease or pneumonitis - If unable to tolerate oral medication10.2.6: Cytomegalovirus (CMV) - CNS disease :

- **Ganciclovir, IV, 5 mg/kg 12 hourly.**

18.6: Retinitis, HIV CMV - If valganciclovir is not available:

- **Ganciclovir, intravitreal, 2 mg twice a week for three weeks then once a week (specialist).**

GENTAMICIN A

3.5: Endocarditis, infective, empiric therapy (native valve and prosthetic valve):

- **Gentamicin, IV, 1.5 mg/kg 12 hourly.**

3.5: Endocarditis, infective, streptococcal directed therapy (native valve) - moderately susceptible, 3.5: Endocarditis, infective, streptococcal directed therapy (native valve) - fully resistant 3.5: Endocarditis, infective, enterococcal directed therapy (native valve) - susceptible to penicillin:

- **Gentamicin, IV, 3 mg/kg daily.**

7.3.2: Urinary tract infection (UTI) - uncomplicated community acquired cystitis:

- **Gentamicin, IM, 5 mg/kg as a single dose.**

14.8.1: Meningitis: Listeria monocytogenes meningitis:

- **Gentamicin, IV, 5 mg/kg daily for 7 days (may be prolonged if response is poor).**

2.2: Febrile neutropenia, 5.3: Pelvic Inflammatory Disease (PID), stage II-IV: severe penicillin allergy, 5.8.4: Septic miscarriage (severe penicillin allergy), 6.19.2: Pyelonephritis, acute, 7.3.2: Urinary tract infection (UTI), acute pyelonephritis: normal renal function, 8.7.3: Diabetic foot ulcers – severe penicillin allergy, 9.3: Brucellosis, 11: Surgical antibiotic prophylaxis,

- **Gentamicin, IV, 6 mg/kg, daily.**

11: Gastrointestinal surgery, urology procedures (clean-contaminated), and obstetric/gynaecological surgery (hysterectomy, laparotomy procedures, vaginal repair), 23.10.3 Sepsis In ICU: Antimicrobial therapy:

- **Gentamicin IV**

IMIPENEM W

2.2: Febrile neutropenia For patients with febrile neutropenia that develop after 48 hours of admission – also consider local susceptibility patterns, 9.1.3: Hospital-acquired pneumonia (HAP)and ventilator-associated pneumonia (VAP):

- **Imipenem/cilastatin, IV, 1000/1000 mg 8 hourly.**

ISONIAZID

10.1.1: Management of selected antiretroviral ADRs, Hepatitis in patients on ART and anti-tuberculosis therapy, 10.2.1: Tuberculosis preventive therapy (TPT):

- **Isoniazid, oral 300 mg daily.**

LEVOFLOXACIN W

10.1.1: Management of selected antiretroviral adverse drug reactions, Hepatitis in patients on ART and anti-tuberculosis therapy, 16.11.1: Confirmed isoniazid monoresistant TB and contraindication to isoniazid:

- **Levofloxacin 750–1000 mg daily.**

LINEZOLID R

10.1.1 Management of selected antiretroviral adverse drug reactions -Hepatitis in patients on ART and anti-tuberculosis therapy:
Linezolid, oral, 600mg daily

MEROPENEM W

2.2: Febrile neutropenia:

- **Meropenem, IV, 1 g 8 hourly.**

23.10.3 Sepsis In ICU: Antimicrobial therapy:

- **Meropenem, IV,** 1 g infusion given over 4 hours, 6 hourly dosing interval.

14.8.1: Meningitis - pneumococcal meningitis and haemophilus influenzae severe penicillin allergy, 9.1.3: Hospital-acquired pneumonia (HAP) and ventilator-associated pneumonia (VAP):

- **Meropenem, IV, 2 g 8 hourly.**

METRONIDAZOLE A

1.3.4: Clostridum difficile (clostridioides difficile) diarrhoea, mild to moderate infection, 14.8.4: Brain abscess:
:

- **Metronidazole, oral, 400 mg 8 hourly.**

1.1.8: Peptic ulcer, H. pylori eradication - For severe penicillin allergy, 5.3: Pelvic Inflammatory Disease (PID), stage I, including severe penicillin allergy:

- **Metronidazole, oral, 400 mg 12 hourly for 7 days.**

1.2.6: Liver abscess, amoebic, 1.3.5: Amoebic dysentery:

- **Metronidazole, oral, 800 mg 8 hourly for 10 days.**

1.3.6: Giardiasis, 5.10: Sexual assault, 10.5.2: Non occupational post exposure prophylaxis, sexual assault - STI Prophylaxis:

- **Metronidazole, oral, 2 g.**

11: Gastrointestinal surgery, 11: Obstetrics/ gynaecology surgery, 11: Otorhinolaryngology/ Head and neck surgery, 11: Urology, 11: Thoracic surgery; 11: Vascular surgery:

- **Metronidazole, IV, 500 mg.**

1.3.4: Clostridum difficile (clostridioides difficile) diarrhoea, 5.3: Pelvic Inflammatory Disease (PID), stage II-IV, 9.1.2: Surgical wound infections, female uro-genital tract, open GIT surgery, 9.9: Tetanus, 14.8.4: Brain abscess:

- **Metronidazole, IV, 500 mg, 8 hourly.**

23.10.3: Sepsis In ICU: Antimicrobial Therapy

- **Metronidazole**

24.6: Malodorous fungating wounds/tumours:

- **Topical metronidazole.**

MOXIFLOXACIN W

16.3 Bronchiectasis if pseudomonas infection is confirmed on culture, if penicillin allergic and unable to tolerate oral therapy, 16.5: Lung abscess, severe penicillin allergy 16.6: Pneumonia, community acquired, severe penicillin allergy, 16.7: Pneumonia, aspiration, severe penicillin allergy, 16.8: Empyema, severe penicillin allergy (and not a complication of pneumonia):

- **Moxifloxacin, IV, 400 mg daily**

10.2.2: Management of selected antiretroviral adverse drug reactions, Hepatitis in patients on ART and anti-tuberculosis therapy, 16.3 Bronchiectasis if pseudomonas infection is confirmed on culture, if penicillin allergyic and able to

switch to oral treatment once, 16.5: Lung abscess, severe penicillin allergy 16.6: Pneumonia, community acquired, without severe features co-morbid patients >65 severe penicillin allergy, 16.7: Pneumonia, aspiration, severe penicillin allergy, 16.8: Empyema, severe penicillin allergy (and not a complication of pneumonia):

- **Moxifloxacin, oral, 400 mg daily.**

NATAMYCIN

18.5.2: Keratitis, suppurative, fungal infection:

- **Natamycin 5%, ophthalmic drops.**

NITROFURANTOIN A

6.19.1: Cystitis; 7.3.2: Urinary tract infection (UTI) - uncomplicated community acquired cystitis and pregnant women:

- **Nitrofurantoin, oral, 100 mg 6 hourly for 5 days.**

PHENOXYMETHYLPENICILLIN A

3.7: Rheumatic heart disease, prophylaxis - All patients with confirmed rheumatic fever and persistent rheumatic valvular disease:

- **Phenoxymethylpenicillin, oral, 250 mg 12 hourly.**

6.7: Syphilis, penicillin desensitisation:

- **Phenoxymethylpenicillin, oral, 250 mg/5 mL.**

PIPERACILLIN/TAZOBACTAM W

2.2: Febrile neutropenia:

Piperacillin/tazobactam, IV, 4.5 g 6 hourly.

9.1.2: Surgical wound infections - If organism is gram negative, 9.1.3: Hospital-acquired pneumonia (HAP) and ventilator-associated pneumonia (VAP):

- **Piperacillin/tazobactam, IV, 4.5 g 8 hourly.**

23.10.3 Sepsis in ICU: Antimicrobial therapy:

- **Piperacillin/tazobactam, IV, 4.5 g infusion given over 4 hours, 6 hourly dosing intervals.**

PROCAINE PENICILLIN A

6.7: Syphilis, symptomatic baby:

- **Procaine penicillin, IM, 50 000 units/kg daily for 10 days (Not for I.V. use).**

PYRAZINAMIDE

10.1.1: Management of selected antiretroviral adverse drug reactions, hepatitis in patients on ART and anti-tuberculosis therapy, 16.11.1: Confirmed isoniazid monoresistant TB AND contraindication to isoniazid:

- **Pyrazinamide, oral, 25 mg/kg daily.**

RIFABUTIN

10.1: Antiretroviral therapy, ART interactions with rifampicin and recommendations for administration - In patients on atazanavir or darunavir, or if double dose LPV/r is not tolerated, replace rifampicin:

- **Rifabutin, oral, 150 mg daily.**

RIFAMPICIN W

3.5: Endocarditis, infective – Emperic therapy – prosthetic valve, 9.3: Brucellosis:

- **Rifampicin, oral, 7.5 mg/kg 12 hourly for 6 weeks.**

16.11.1: Isioniazid monoresistant TB - Confirmed isoniazid monoresistant TB and contraindication to isoniazid:

- **Rifampicin, oral, 10 mg/kg daily.**

10.1.1: Management of selected antiretroviral adverse drug reactions, hepatitis in patients on ART and anti-tuberculosis therapy; <60kg:

- **Rifampicin, oral 450 mg daily.**

10.1.1: Management of selected antiretroviral adverse drug reactions, hepatitis in patients on ART and anti-tuberculosis therapy:

- **Rifampicin, oral 600 mg daily.**

RIFAMPICIN/ISONIAZID W

16.9: Tuberculosis, pulmonary, continuation phase: 30-37kg, 16.10: Tuberculosis, pleural, continuation phase (TB Pleurisy): 30-37kg:

- **Rifampicin/isoniazid, oral, 300/150 mg, daily for 4 months.**

16.9: Tuberculosis, pulmonary, continuation phase: 38-54kg, 16.10: Tuberculosis, Pleural, continuation phase (TB Pleurisy): 38-54kg:

- **Rifampicin/isoniazid, oral, 450/225 mg, daily for 4 months.**

16.9: Tuberculosis, pulmonary, continuation phase: >55kg, 16.10: Tuberculosis, Pleural, continuation phase (TB Pleurisy): >55kg:

- **Rifampicin/isoniazid, oral, 600/300 mg, daily for 4 months.**

RIFAMPICIN/ISONIAZID/PYRAZINAMIDE/ETHAMBUTOL W

16.9: Tuberculosis, pulmonary, initial phase: 30-37kg, 16.10: Tuberculosis, pleural (TB pleurisy): 30-37kg, 16.11.1: Isoniazid monoresistant TB: 30-37kg:

- **Rifampicin/isoniazid/pyrazinamide/ethambutol, oral, 300/150/800/550 mg, daily for 2 months.**

16.9: Tuberculosis, pulmonary, initial phase: 38-54kg:16.10: Tuberculosis, pleural (TB pleurisy): 38-54kg, 16.11.1: Isoniazid monoresistant TB: 38-54kg:

- **Rifampicin/isoniazid/pyrazinamide/ethambutol, oral, 450/225/1200/825 mg, daily for 2 months.**

16.9: Tuberculosis, pulmonary, initial phase:55-70kg, 16.10: Tuberculosis, pleural (TB pleurisy):55-70kg, 16.11.1: Isoniazid monoresistant TB :55-70kg:

- **Rifampicin/isoniazid/pyrazinamide/ethambutol, oral, 600/300/1600/1100 mg, daily for 2 months.**

16.9: Tuberculosis, pulmonary, initial phase:71kg and over, 16.10: Tuberculosis, Pleural, initial phase:71kg and over, 16.11.1: Isoniazid monoresistant TB: >71kg:

- **Rifampicin/isoniazid/pyrazinamide/ethambutol, oral, 750/375/2000/1375 mg, daily for 2months.**

TENOFIVIR ALAFENAMIDE (TAF)

1.2.4.2: Hepatitis B, chronic (non-HIV co-infection) - If eGFR 15-50mL/min (or on haemodialysis):

- **Tenofovir, oral, 25 mg daily.**

TENOFOVIR DISOPROXIL FUMARATE (TDF)

1.2.4.2: Hepatitis B, chronic (non-HIV co-infection) - eGFR > 50mL/min:

- **Tenofovir, oral, 300 mg daily.**

VALGANCICLOVIR

10.2.6: Cytomegalovirus (CMV) - Biopsy-proven GIT disease or pneumonitis and CNS disease, 18.6: Retinitis, HIV CMV:

- **Valganciclovir, oral, 900 mg 12 hourly for 3 weeks, then 900 mg daily until immune recovery (CD4 >100 cells/mm^3 on ART).**

VANCOMYCIN W

1.3.4: Clostridium difficile (Clostridioides difficile) diarrhoea:

- **Vancomycin, oral, 125 mg. (Give the parenteral formulation orally).**

18.2: Endophthalmitis, bacterial - Endogenous endophthalmitis and post-surgical endophthalmitis:

- **Vancomycin, intravitreal, 1 mg.**

3.5: Endocarditis, infective - Antibiotic therapy - severe penicillin-allergic patients, or methicillin resistant staphylococcal infections, 3.5: Endocarditis, infective – Empiric therapy - prosthetic valve, 3.5: Endocarditis, infective - Directed therapy (native valve) - Fully resistant, 3.5: Endocarditis, infective - Staphylococcal - Cloxacillin-resistant (methicillin resistant) or methicillin sensitive with significant beta-lactam allergy:

- **Vancomycin, IV, 15-20 mg/kg 12 hourly.**

2.2: Febrile neutropenia, IV, skin infection, 9.1.1: Intravascular catheter infections, S. aureus infection, 9.1.2: Surgical wound infections, Methicillin (cloxacillin) resistant S. aureus (MRSA):

- **Vancomycin, IV, 25-30 mg/kg as a loading dose. Follow with 15-20 mg/kg/dose 12 hourly.**

23.10.3 Sepsis in ICU: Antimicrobial therapy.

- **Vancomycin.**

AMIKACIN, IV

- Amikacin, IV, 15 mg/kg daily given slowly over 30 minutes.
  - If BMI is >40 kg/m^2 use ideal body weight* + 40% of the difference between ideal and actual body weight.
  - In severe sepsis or septic shock, a loading dose of 25 mg/kg should be given (irrespective of renal function).
  - If eGFR is 40–60 mL/minute, adjust maintenance dose to 15 mg/kg every 36 hours (check trough amikacin level and give the next dose when level is <5 mg/L or be guided by local laboratory cut off trough value).
  - Maximum daily dose 1.5 g, usually for a maximum of 10 days.
  - Amikacin is nephrotoxic and ototoxic – monitor creatinine three times per week and discontinue if vestibular or cochlear symptoms develop. Regular audiometry is essential with longer term use in patients with drug-resistant TB.
  - Therapeutic drug monitoring: pre-dose amikacin trough levels after the third dose. Aim for a trough level of <5 mg/L or be guided by local laboratory cut off trough value.
    - Normal renal function: do not wait for the amikacin level before giving the next dose. The level should be used to adjust the dose for the next day if applicable.
    - Impaired renal function: wait for the amikacin level and give the next dose when level is <5 mg/L.
    - In obese patients or in patients with resistant Gram-negative bacteria also measure peak concentrations (0.5–1 hour after infusion). Aim for peak of >30 mg/L (or ten times higher than the MIC for resistant organisms).

      ** Ideal body weight calculator:* https://www.mdcalc.com/ideal-body-weight-adjusted-body-weight

AMIODARONE, ORAL

- Amiodarone, oral, 800 mg daily for 7 days.
  - Then 600 mg daily for 3 days.
  - Hypotension may occur, especially during the loading dose phase
  - Titrate to maintenance dose of 200–400 mg daily.
  - May cause hypothyroidism or thyrotoxicosis - monitor thyroid function every 6 months.
  - Monitor for pulmonary symptoms and perform baseline CXR before starting long-term therapy and annually thereafter to monitor for interstitial pulmonary fibrosis.
  - In chronic use, liver function tests and tests for hypokalaemia (if on diuretic) should be conducted periodically.

AMOXICILLIN/CLAVULANIC ACID, ORAL

- Amoxicillin/clavulanic acid, oral, 875/125 mg (containing 875 mg amoxicillin trihydrate and 125 mg clavulanic acid) 12 hourly.
  - When treating pneumonia in areas where there is a confirmed high prevalence (≥ 5%) of *Streptococcus pneumoniae* with intermediate resistance to penicillin: dose 8 hourly
    ADD: Amoxicillin 1 g, oral, daily between the amoxicillin/clavulanic acid doses (i.e. 8 hours after the morning dose of amoxicillin/clavulanic acid).

AMOXICILLIN/CLAVULANIC ACID, IV

Amoxicillin/clavulanic acid IV is not suitable for intramuscular or subcutaneous administration.

- Amoxicillin/clavulanic acid, 1.2 g powder vials for intravenous injection containing amoxicillin sodium equivalent to 1 g of amoxicillin and potassium clavulanate equivalent to 200 mg clavulanic acid.
  - **Dosage Recommendation:** Amoxicillin/clavulanic acid, 1.2 g, IV, 8 hourly.
  - **Directions for use:**
    - Powder vials for injection can be reconstituted by dissolving in 20 mL water for injection.
    - Reconstituted vials can be administered intravenously by injection over 2 minutes or slow intravenous infusion over 30 minutes.
    - For intravenous infusion, the reconstituted vial should be further diluted with the desired volume of a suitable infusion fluid (e.g. Sodium chloride 0.9%, 100 mL).
    - **The contents of the vials must be used within 20 minutes.**
  - **Precautions:**
    - Allergy to penicillins.
    - Drug-induced cholestatic hepatitis may occur, typically a few weeks after starting therapy. Use with caution in patients with evidence of hepatic dysfunction.
    - Dosage adjustments required in renal impairment:
      - CrCl >70 mL/minute: no dose adjustment required.
      - CrCl 10–30 mL/minute: 1.2 g as a single dose followed by 600 mg 12 hourly.
      - CrCl <10 mL/minute: 1.2 g as a single dose followed by 600 mg daily.

AMPHOTERICIN B DEOXYCHOLATE, IV

- Amphotericin B deoxycholate, IV, 0.7–1 mg/kg daily, dose and duration of therapy depend on indication for use and infecting organism. Daily dose must not exceed 1.5mg/kg.

  - Reconstitue in 5% dextrose only (as incompatibile with saline solution). Do not reconstitute or dilute with saline or administer through an

intravenous line that has previously been used for saline, unless first flushed with dextrose solution (5 %,10 % or 20 %) for infusion.
  - Administer over a period of 2–6 hours.
  - Ensure adequate hydration, by loading with 0.9% normal saline, to minimise the risk of nephrotoxicity.
- Treat infusion reactions with hydrocortisone 25mg IV. In such cases, premedicate with hydrocortisone 25mg IV and paracetamol 1g orally, half an hour before each dose, until tolerance develops.

Monitoring

- Serum potassium, magnesium and creatinine (baseline and twice weekly). Monitoring of serum potassium and creatinine should occur more frequently in neutropenic patients (3 times a week).
- Monitor haemoglobin (baseline and weekly).
- Careful attention to fluid monitoring of intake and output.
- For management of hypokalaemia, see section 7.2.2: Hypokalaemia.
- Monitor drip sites and replace if any evidence of phlebitis.

Management of elevated creatinine in cryptococcal meningitis

If creatinine increases by ≥2 fold from baseline value, stop amphotericin B deoxycholate, increase pre-hydration to 1 litre 8 hourly (watch for fluid overload), and switch to fluconazole 600mg daily and flucytosine 25mg/kg (with the flucytosine dosing interval adjusted for eGFR).

- Once improved, restart to complete 7 days amphotericin B deoxycholate in total
- (Adapted from: WHO. Rapid advice: diagnosis, prevention and management of cryptococcal disease in HIV-infected adults, adolescents and children: Prevention, monitoring and management of amphotericin B toxicity. 2011 [Online] [Accessed March 2016] http://www.ncbi.nlm.nih.gov/books/NBK299520/pdf/Bookshelf_NBK299520.pdf

Management of elevated creatinine for fungal infections other than cyptococcal meningitis

If creatinine increases by ≥2 fold from baseline value, either omit an amphotericin B dose, or increase pre-hydration to 1 litre 8 hourly.

- Once improved, restart at 0.7 mg/kg daily and consider alternate day amphotericin B.
- If creatinine remains elevated i.e. ≥2 fold from baseline value, discontinue amphotericin B and continue with fluconazole, oral, 800 mg daily (for fungal infections known to be responsive to fluconazole, e.g. *Cryptococcus*).

  (Adapted from: WHO. Rapid advice: diagnosis, prevention and management of cryptococcal disease in HIV-infected adults, adolescents and children: Prevention, monitoring and

management of amphotericin B toxicity. 2011 [Online] [Accessed March 2016] http://www.ncbi.nlm.nih.gov/books/NBK299520/pdf/Bookshelf_NBK299520.pdf

LIPOSOMAL AMPHOTERICIN B, IV

- Liposomal amphotericin B, IV, 10 mg/kg single dose for cryptococcal meningitis
  - Reconstitue in 5% dextrose only (as incompatibile with saline solution). Do not reconstitute or dilute with saline or administer through an intravenous line that has previously been used for saline unless first flushed with dextrose solution (5 %,10 % or 20 %) for infusion.
  - Administer over a period of 2 hours.
  - Liposomal amphotericin B contains soya oil. Patients allergic to peanut or soya should not be given liposomal amphotericin B.

Monitoring in patients with cryptococcal meningitis

- Anaphylaxis and anaphylactoid reactions have been reported in association with liposomal amphotericin B. If a severe anaphylactic/ anaphylactoid reaction occurs, the infusion should be immediately discontinued and the patient should not receive further infusion.
- Monitor blood glucose levels in diabetic patients - each vial of liposomal amphotericin B contains 900mg of sucrose. Furthermore, liposomal amphotericin B must be reconstituted with dextrose 5%.

CEFEPIME, IV

- Cefepime IV/IM, 1–2 g 12 hourly.
  - Renal adjusted dosing:
    - eGFR >50 mL/minute: 100% of daily dose
    - eGFR 10–50 mL/minute: 50–100% of daily dose
    - eGFR <10 mL/minute: 25–50% of daily dose

      (Source: *Bennet, WM. Drug prescribing in renal failure. Fifth edition*).

CLINDAMYCIN, IV

- Clindamycin IV, 600 mg, 8 hourly (maximum of 4.8 g/day)
  - Dilute the contents of the vial in 100 mL of diluent prior to infusion.
  - Infuse over 20 minutes.
  - **Note:** Rapid infusion can cause flushing, pain, thrombophlebitis, hypotension and cardiopulmonary arrest.
  - Local pain at injection site may be minimised by deep IM injection. Not more than 600mg should be injected into a single IM injection site.

DIGOXIN, ORAL

- Digoxin, oral, 0.125 mg daily, adjust according to rate response, if in atrial fibrillation, and trough plasma level.
  - Digoxin trough plasma levels (before the morning dose) should be maintained between 0.6–1 nmol/L. Monitor after 7 days and periodically thereafter.
  - Patients at high risk of digoxin toxicity are:
    - the elderly,
    - patients with renal dysfunction,
    - hypokalaemia,
    - hypomagnesaemia,
    - hypercalcaemia and
    - patients with low lean body mass.

FLUCYTOSINE, ORAL

- Flucytosine, oral, 25 mg/kg 6 hourly for 14 days for cryptococcal meningitis.

Monitoring

- Flucytosine is partially metabolised to 5-fluorouracil which is potentially teratogenic. Women of childbearing age should be counselled on effective contraception during treatment and up to one month following discontinuation of treatment. Male patients should be counselled to use effective contraception during treatment and for 3 months following discontinuation of flucytosine treatment.

Management of elevated creatinine

Dosage adjustment is required in patients with renal impariment as tabulated below:

Creatinine Clearance	Single Dose	Dosing Interval
CrCl >40mL/min	25mg/kg	6 hourly
20 ≤ CrCl < 40mL/min	25mg/kg	12 hourly
10 ≤ CrCl < 20mL/min	25mg/kg	24 hourly
CrCl <10mL/min*	25mg/kg	48 hourly

***Adopted from:** Flucytosine | Johns Hopkins ABX Guide (hopkinsguides.com) https://www.hopkinsguides.com/hopkins/view/Johns_Hopkins_ABX_Guide/540227/all/Flucytosine?q=flucytosine#3.2 and *Govender NP, Meintjes G, Mangena P, Nel J, Potgieter S, et al. Southern African HIV Clinicians Society guideline for the prevention, diagnosis and management of cryptococcal*

disease among HIV-infected persons: 2019 update. South Afr J HIV Med. 2019 Nov 8;20(1):1030. https://pubmed.ncbi.nlm.nih.gov/32201629/ Source: The Sanford guide to antimicrobial therapy 2019 / editors, David N, Gilbert MD, George M, Eliopoulos MD, Henry F, Chambers MD et al. Sperryville, VA, USA: Antimicrobial Therapy, Inc., [2019]).

GENTAMICIN, IV

- Gentamicin, IV, 5–6 mg/kg once daily.
  - If BMI is >40 kg/m^2 use ideal body weight* + 40% of the difference between ideal and actual body weight.
  - Administer slowly over 3 minutes or infused over 20–30 minutes up to 2 hours, diluted in 5% dextrose or 0.9% sodium chloride solution.
  - For streptococcal endocarditis: 1.5 mg/kg 12 hourly (in combination with penicillin).
  - Renal impairment dosage adjustment (eGFR <60 mL/minute):
    - Administer 3–4 mg/kg loading dose and adjust further dosing according to plasma concentrations.
  - Gentamicin is potentially nephrotoxic and ototoxic – monitor creatinine three times per week and discontinue if vestibular or cochlear symptoms develop.
  - Therapeutic drug monitoring: Sample after the third dose;
    - Draw trough concentrations immediately before dose; peak concentrations 0.5–1.0 hours after dosing from the drip-free arm.
    - Therapeutic ranges: Peak >8 mcg/ml, trough <1 mcg/ml
    - Reduce the dose per kg or consider omitting a dose if concentration is supratherapeutic. If the plasma concentration is subtherapeutic but the patient has signs of toxicity, change to an alternative agent.

      ** Ideal body weight calculator:* https://www.mdcalc.com/ideal-body-weight-adjusted-body-weight

LABETALOL, IV

- Labetalol, IV infusion, 2 mg/minute to a total of 1–2 mg/kg.
  - Initial dose: 2 mg/minute
  - Titrate to response up to 300 mg total cumulative dose (e.g. discontinue after 2.5 hours of 2 mg/minute).
  - Usual total dose required is 50–200 mg (1–2 mg/kg).
  - Commence an oral antihypertensive regimen as soon as the infusion is discontinued.

LITHIUM, ORAL

- Lithium, oral, 400mg at night.
  - Check eGFR and thyroid function before starting lithium. Lithium may be used once hypothyroidism is treated. Adjust doses if renal function is impaired and, in the elderly, as below.
  - Start with 400mg (200mg in the elderly) at night. Check the plasma level after 7 days and adjust dose as needed (usually by 200–250mg). Check plasma levels 7 days after each dose adjustment until desired plasma

level is reached. *(Adopted from: Maudsley prescribing guidelines in psychiatry / David M. Taylor, Thomas R. E. Barnes, Allan H. Young. 13th edition. | Hoboken, NJ : Wiley, 2019.)*

- Dose-adjust in renal impairment:
  - CrCl ≥ 60 mL/minute: Normal daily dose (see above).
  - CrCl 30 to < 60 mL/minute: Initiate at low doses (e.g., 150 to 300 mg/day) in 1 to 2 divided doses, titrate slowly based on clinical response and tolerability, monitor levels frequently.
  - CrCl < 30 mL/minute: Avoid Use.

Adapted from Up to Date: Dosing: Kidney Impairment: Adult (Lithium). Available at: https://www.uptodate.com/

- Lithium has a narrow therapeutic window. The therapeutic range is 0.4–0.8 mmol/L for maintenance therapy, and 0.8–1.0 mmol/L in acute mania.
- Measure serum concentrations at 12 hours after the last dose. Note the time of blood specimen collection and the time of the last dose on the laboratory request form to facilitate accurate reference range and interpretation.
- Maintain therapeutic blood levels of lithium for as long as the patient is on lithium. Monitor lithium levels and renal function monthly for the first 3 months of therapy.
- Monitoring once stable levels have been achieved: Lithium levels, eGFR and TSH 6-monthly. Serum calcium (for lithium-induced hyperparathyroidism) annually.
- Lithium induced hypothyroidism is treated with thyroxine (note that TFTs usually normalise if lithium is discontinued).
- **Beware of combining lithium with ACE-inhibitors, NSAIDs and thiazide diuretics, as they all potentiate the risk for lithium toxicity**.
- Pregnancy - Lithium has been associated with congenital abnormalities in the newborn with first trimester exposure. Women of child-bearing potential should be on contraception. Risk-benefit assessment required for indication of maternal use during pregnancy.
- Discontinuation: abrupt discontinuation may precipitate a manic episode in the first few months after stopping lithium. Adherence support is important. Planned discontinuation should be gradual, over at least a month, with reductions of plasma levels by about 0.2 mmol/L at a time.

METFORMIN, ORAL

- Metformin, oral, 500 mg twice daily with meals.
  - Titrate dose slowly depending on HbA_{1c} and/or fasting blood glucose levels to a maximum dose of 850 mg 8 hourly.
  - Monitor renal function.
  - Dose-adjust in renal impairment as follows:
    - eGFR > 60 mL/minute: Normal daily dose (see above).

  - eGFR < 60 mL/minute: Half of the daily dose.
  - eGFR < 30 mL/minute: Stop metformin.
- Contra-indicated in:
  - renal impairment i.e. eGFR < 30 mL/minute,
  - uncontrolled congestive cardiac failure,
  - severe liver disease,
  - patients with significant respiratory compromise, or
  - peri-operative cases.
- Drug-drug interaction with dolutegravir (DTG): DTG may increase the serum concentration of metformin. Limit maximum dose of metformin to ≤ 2 g per day if concomitant use with DTG.

MORPHINE, IV

- Morphine, IV, to a maximum dose of 10 mg.
  - Morphine, IV, 3–5 mg as a single dose then further boluses at intervals of 5–10 minutes and monitor all vitals closely.
  - Dilute 10 mg up to 10 mL with sodium chloride 0.9%.
  - Repeat after 4 hours if necessary.
  - Monitor response to pain and effects on respiration and blood pressure.
  - Onset of action: 5–10 minutes. Duration of action: 4-5 hours.

PHENYTOIN, IV

- Phenytoin, IV, 20 mg/kg diluted in sodium chloride 0.9% **(not dextrose)** administered not faster than 50 mg/minute, with cardiac monitoring. Elderly patients and patients with impaired liver function, require lower doses initially with subsequent adjustment. IV administration in the elderly and patients with impaired liver function should not exceed 25mg/minute (possibly as little as 5-10mg/minute).
  - Mixing instructions: For preparation of the infusion, the contents of a vial of phenytoin should be well mixed in 0.9% sodium chloride at a concentration of less than 4 g/L and be completely administered within 1 hour of mixing to avoid precipitation.
  - Cardiac monitoring should be done during the infusion.
  - If dysrhythmias occur, interrupt the infusion temporarily and reintroduce slowly, once rhythm becomes stable.
  - Continue with, IV, 5 mg/kg/day (300 mg daily for most adults).

POTASSIUM CHLORIDE, IV

Must always be diluted before infusion.

- Potassium chloride, IV, diluted in 1 L sodium chloride 0.9%.
  - Rapid infusion of potassium chloride can cause fatal dysrhythmias.
  - Infusion rates > 20 mmol/hour are very irritating to peripheral veins.
  - Potassium chloride 15% for intravenous use, contains 20 mmol K+ per 10 mL ampoule.

- Potassium chloride infusion – see diabetes section for the administration of potassium infusion in DKA (Section 8.6.2: Diabetic ketoacidosis (DKA) and hyperosmolar hyperglycaemic state (HHS)).
- Non DKA; Dilute potassium chloride in a non-glucose containing solution (e.g. 0.9% sodium chloride) to a concentration not exceeding 40 mmol/L. Maximum rate of infusion should not exceed 20 mmol/ hour. Total daily dose should not exceed 3mmol/kg/day (max 400mmol/day).
- As large volumes of solution may need to be given, monitor the patient for fluid overload.
- For preparation of the infusion, the contents of an ampoule of potassium chloride should be well mixed in 0.9% sodium chloride.

An example prescription might be: '*dilute two 10 ml ampoules of 20 mmol KCl in 1 litre of 0.9% sodium chloride, and mix thoroughly. Infuse at a rate of 125 ml/hour, and repeat 8 hourly (i.e. give three litres of the solution containing 40 mmol KCl per litre as a constant infusion over a 24 hour period)*'.

PREDNISONE, ORAL

Prednisone tapering - generally required after prolonged use (i.e. >1 week)

- Example of a dose reduction regimen: for an initial dose of 60 mg daily, reduce initial dose to 2/3 the original dose, and continue as follows:
  - » 40 mg/day in week 2,
  - » 25 mg/day in week 3,
  - » 20 mg/day in week 4,
  - » 15 mg/day in week 5,
  - » 10 mg /day in week 6 and
  - » thereafter 5 mg daily for 1 week and then discontinue.

Note: Weaning should be adjusted according to clinical context. If control deteriorates on weaning return to the previous effective dose.

VANCOMYCIN, IV

- Vancomycin, IV, 25-30 mg/kg as a loading dose. Follow with 15-20 mg/kg/dose 12 hourly. Duration depends on the organism & site of infection: for methicillin-resistant *Staphylococcus aureus* duration is 2 weeks after first negative blood culture, or 4 weeks for complicated infections (e.g., endocarditis).
  - The rate of infusion should not exceed 1 g/hour (i.e., at least 2 hours for a 2 g infusion).
  - **Note:** Rapid infusion can cause flushing, pain, thrombophlebitis, hypotension and cardiopulmonary arrest.
  - Weigh patients and estimate eGFR (see chapter 7: Nephrological/ urological disorders).

- See table for dosing interval and measurement of trough concentrations.
- Aim for trough concentration of 10–20 mcg/mL except in osteitis or endocarditis or if MIC > 1 when trough should be 15–20 mcg/mL.
- If trough is too low, increase dose (specialist consultation if unsure how much to increase) and/or shorten dose interval to 8 hourly.
- If trough too high, decrease dose or increase dosing interval (specialist consultation if unsure how much to adjust).
- Vancomycin is not significantly removed by conventional intermittent haemodialysis. Dosing and monitoring as for those with eGFR <25 mL/minute.

Dosing intervals and when to measure trough concentrations of vancomycin:

eGFR (mL/minute)	**Dosing interval (hours)**	**Measurement of trough concentrations**
>80	12	Before 3rd dose
50-79	24	Before 3rd dose
35-49	36	Before 2nd dose
25-34	48	Before 2nd dose
<25 **or** haemodialysis **or** CAPD	When trough level <15	3 days after loading dose

(Adapted with permission from Groote Schuur hospital's protocol).

WARFARIN, oral

- Warfarin, oral, 5 mg daily adjusted to maintain INR between 2 and 3.
  - *Warfarin interactions:*
    A large number of medicines interact with warfarin leading to under- or over-anticoagulation, and careful evaluation of all new medicines, herbal and over-the counter products is critical. This includes (but is not an exhaustive list):
    - Medicines altering platelet function e.g., NSAIDs, aspirin, clopidogrel, etc.
    - Food (e.g. cruciferous vegetables) or medicines (e.g. antibiotics) altering vitamin K synthesis
    - Medicines interfering with warfarin metabolism e.g. efavirenz, rifampicin, macrolide antibiotics, simvastatin, phenytoin, carbamazepine, Imidazoles (ketoconazole, fluconazole, itraconazole, miconazole) quinolones, co-trimoxazole, selective serotonin reuptake inhibitors (SSRIs), glibenclamide etc.

- Grapefruit juice St John's wort (commonly used herbal preparation), Ginkgo biloba and garlic

Unless INR is markedly out of range the modest adjustments recorded below should be followed:

Initiation

Warfarin initiation dosing protocol (week 1) with INR target: 2–3		
Day therapy	**INR Value**	**Total daily dose**
Day 1		5 mg daily (2.5 mg daily for high sensitivity)
2 to 3 days after initiation	< 1.5 1.5 – 1.9 2.0 – 2.5 > 2.5	5–7.5 mg daily 2.5–5 mg daily 2.5 mg daily Hold warfarin and recheck INR next day
2 to 3 days after last INR check	< 1.5 1.5 – 1.9 2.0 – 3.0 > 3.0	7.5–10 mg daily 5–10 mg daily 2.5–5 mg daily Hold warfarin and recheck INR in1–2 days

Frequency of INR monitoring after initiation of warfarin	
Check INR	
Every 2–3 days	Until INR within therapeutic range on 2 consecutive INR checks
Then every week	Until INR within therapeutic range on 2 consecutive INR checks
Then every 2 weeks	Until INR within therapeutic range on 2 consecutive INR checks
Then every 4 weeks	When dose is stable, check monthly

Maintenance

Warfarin maintenance dosing protocol to maintain an INR 2-3:

INR<1.5	INR: 1.5-1.9	INR: 2.0-3.0	INR: 3.1-4.0	INR: 4.1-5	INR: 5.1-9.0	INR>9.0
Extra Dose. Increase **weekly** dose 10%.	Increase **weekly** dose 5%.	No change.	Decrease **weekly** dose 5%.	Withhold 1 dose. Decrease **weekly** dose 10%.	*Withold 2 doses. Decrease **weekly** dose 20%.	Admit.

*History and examination to exclude bleeding. Admit persons with additional risks for bleeding.

Frequency of INR monitoring for maintenance of warfarin	
Check INR	
Every 3–5 days	If start/stop interacting medication, change in diet, change in activity level or other change that could affect INR.
Every 1–2 weeks	Once INR within therapeutic range on 2 consecutive INR checks.
Every 4 weeks	If maintained on same stable dose < 6 months and INR stable.
Every 6–8 weeks*	If maintained on same stable dose ≥ 6 months and INR stable.

*A stable INR is when a patient is maintained on the same dose of warfarin for ≥6 months. INR would require to be checked every 6-8 weeks.

Time in therapeutic range (TTR)

The Rosendaal method is commonly used for monitoring and is validated to assess the time in therapeutic range (TTR). A TTR < 65% is associated with poorer outcomes and may signal a re-assessment of patient adherence and dosing.

Source: Rosendaal FR, Cannegieter SC, van der Meer FJ, Briët E. A method to determine the optimal intensity of oral anticoagulant therapy. Thromb Haemost. 1993 Mar 1;69(3):236-9. https://pubmed.ncbi.nlm.nih.gov/8470047/

Rosendaal calculation procedure (preferred method)

Example:

A patient has an INR reading of 2.4 on 1 October and a follow up INR measurement of 3.2 on 17 October.

If the patient's INR moves linearly from 2.4 to 3.2 throughout the 16-day interval, then we can estimate that the patient was within the INR therapeutic range (2 – 3) for approximately 75% of the time interval.

See calculation steps below:

Calculation steps:	Example:
1. Calculate the duration of the time interval between 2 INR values*	1 October to 17 October = 16 days
2. Calculate the amount of total INR shift in the time interval.	INR on 1 October: 2.4 INR on 17 October: 3.2 Total INR shift: 0.8
3. Calculate the amount of INR shift that is within the therapeutic range.	Upper INR threshold = 3.0 INR measurement in range = 2.4 Amount of INR shift within range: 3.0 - 2.4 = 0.6
4. Calculate the percent of total shift that is within therapeutic range. This is the %TTR for this specific time interval.	$\frac{\text{Amount of INR shift within range}}{\text{Total INR shift}}$ = 0.6 /0.8 = 75%
5. Estimate the number of days in the interval that were within the therapeutic range	Duration of INR measurement interval X % TTR = 16 days X 75% = 12 days in therapeutic range
6. To calculate overall %TTR over multiple INR measurements, add total days in range for each time interval and divide by the total period of therapy.	A follow-up INR measurement on 30 October was 2.7. The %TTR for the interval of 17-30 October is 60% and days in therapeutic range is 8 days. The overall days in therapeutic range is 12 days + 8 days and the overall therapeutic period is 16 + 13 days. $\frac{\text{20 days in therapeutic range}}{\text{29 days in treatment period}}$ = 69% cumulative TTR

Adapted from the *Rosendaal Method for % INR in range [Internet]. Using the ROSENDAAL method for calculating therapeutic time in range (TTR). INRpro.com; [cited 2022Nov29]. Available from: https://www.inrpro.com/rosendaal.asp*.

Note:

» The Rosendaal method for calculating TTR is not advised for intervals longer than 56 days/2 months between INR measurements.

» For step 3, if both INR measurements above or if both INR measurements are below the therapeutic range, time spent in therapeutic range is 0 and %TTR is also 0% for that time interval. E.g. first INR = 1.5 and second INR = 1.7

» For step 3, if one INR measurement is below therapeutic range and one is above the therapeutic range, then the INR shift within the therapeutic range will be 1. E.g. first INR = 1.5 and second INR = 3.2.

» For a TTR <65% adherence with warfarin therapy should be assessed and

reinforced with the patient. Adjust the dose of warfarin only once it is established that poor adherence is not the cause of the sub-therapeutic TTR.

Frequency in range (FIR) (alternative to the preferred Rosendaal method, when a simple manual calculation is required).

Warfarin anticoagulation may also be monitored using the frequency in range (FIR) method which performs comparably to the TTR method. FIR should be maintained at a level greater than 54% as this was found to be a good predictor of optimal anticoagulation (TTR >/= 65%).

Soure: Parboo P et al. A comparison between TTR and FIR as a measure of the quality of anticoagulation in patients with atrial fibrillation. Wits Journal of Clinical Medicine, 2019, 1(1) 23–30

The FIR is calculated using the following formula:

$$\text{Frequency in range (\%)} = \frac{\text{Number of tests within therapeutic range}}{\text{Total number of tests performed}}$$

Note:

» The FIR method is less reliable when INR levels are measured at irregular intervals

The South African Medicines Formulary, 14th Edition. Division of Clinical Pharmacology. University of Cape Town, 2022 was used in the update of sections in Appendix II prescribing information for specific medicines.

MEDICINES AND BIRTH DEFECTS

Some medicines are known to cause abnormal fetal development resulting in fetal death or babies born with birth defects. Some of these effects may happen very early in pregnancy, within the first 6 weeks of gestation, before most patients realise they are pregnant. It is therefore important that women who are in their reproductive age and are prescribed any teratogenic medicine should be made aware of the risk and placed on reliable contraception. Some medicines can cause fetal damage in the second or third trimester.

Where possible, stop teratogenic medicines before a pregnancy is planned and prescribe suitable alternatives.

Any medicine that is prescribed during pregnancy must be carefully evaluated, and risk versus benefit should be assessed before use. Refer to prescriber information for details regarding risks in pregnancy. .

Refer pregnancies exposed to teratogenic medicines during the first trimester for a detailed fetal anomaly scan.

The table below lists some commonly used medicines that are associated with birth defects.

MEDICINES	ADVERSE FETAL EFFECTS	*LoE*
Androgens	Masculinisation of the developing female fetus can occur.	*III*[i]
ACE- inhibitors/ ARBs	Fetal hypotension resulting in fetal kidney hypoperfusion and anuria, with fetal growth restriction and demise.	*III*[ii]
Anticonvulsants:		
Carbamazepine	Increases the risk of facial dysmorphology, neural tube defects, cardiovascular defects, and urinary tract defects.	*II*[iii]
Phenytoin	Increases the risk of fetal hydantoin syndrome, consisting of facial dysmorphology, cleft palate, ventricular septal defect, and growth and intellectual disability.	
Valproate	Increases the risk of spina bifida, facial dysmorphology, autism, atrial septal defect, cleft palate, hypospadias, polydactyly, craniosynostosis, limb abnormalities, neurodevelopmental problems (approximately 40%) and autism[iv].	

[i] Androgens:Wilkins L. Masculinization of female fetus due to use of orally given progestins. JAMA. 1960 Mar 5;172(10):1028–32. https://jamanetwork.com/journals/jama/article-abstract/327726

[ii] Hanssens M, Keirse MJ, Vankelecom F, Van Assche FA. Fetal and neonatal effects of treatment with angiotensin-converting enzyme inhibitors in pregnancy. Obstet Gynecol. 1991 Jul;78(1):128–35. https://www.ncbi.nlm.nih.gov/pubmed/2047053

[iii] Anticonvulsants: Weston J, Bromley R, Jackson CF, Adab N, Clayton-Smith J, Greenhalgh J, Hounsome J, McKay AJ, Tudur Smith C, Marson AG. Monotherapy treatment of epilepsy in pregnancy: congenital malformation outcomes in the child. Cochrane Database Syst Rev. 2016 Nov 7;11:CD010224. https://www.ncbi.nlm.nih.gov/pubmed/27819746

[iv] Valproic acid – caution in pregnancy: European Medicines Agency - Pharmacovigilance Risk Assessment Committee. Assessment report EMA/198940/2018 - valproate exposure in pregnancy, 8 February 2018.

Antidepressants	SSRIs should in general be continued during pregnancy and breastfeeding. There is uncertainty in the evidence, but potential complications may include an increased risk of birth defects, postpartum haemorrhage, premature birth and low birth weight.	*III*[v]
Carbimazole	Increased risk of birth defects in the first trimester and at high daily doses of ≥15 mg.	*III*[vi]
Dolutegravir	There is an increased risk of neural tube birth defects involving the brain, spine, and spinal cord; if used within the first 6 weeks of pregnancy.	*III*[vii]
Efavirenz	No increased prevalence of birth defects detected and in a large multi-cohort analysis or from a South African exposure registry.	*I*[viii]
Lithium	First trimester exposure is associated with an increased risk of birth defects.	*II*[ix]
Macrolide	In a large population-based cohort study, when compared to penicillin, first trimester macrolide exposure was associated with increased risk of cardiovascular malformations, and macrolide exposure in any trimester was associated with increased risk of genital malformations. The majority of macrolide exposures in	*III*[x]

http://www.ema.europa.eu/docs/en_GB/document_library/Referrals_document/Valproate_2017_31/Position_provided_by_CMDh/WC500250221.pdf

Valproic acid – caution in pregnancy: Meador K, Reynolds MW, Crean S, Fahrbach K, Probst C. Pregnancy outcomes in women with epilepsy: a systematic review and meta-analysis of published pregnancy registries and cohorts. Epilepsy Res. 2008 Sep;81(1):1-13. https://www.ncbi.nlm.nih.gov/pubmed/18565732

[v] Antidepressants: ACOG Committee on Practice Bulletins--Obstetrics. ACOG Practice Bulletin: Clinical management guidelines for obstetrician-gynecologists number 92, April 2008 (replaces practice bulletin number 87, November 2007). Use of psychiatric medications during pregnancy and lactation. Obstet Gynecol. 2008 Apr;111(4):1001–20. https://www.ncbi.nlm.nih.gov/pubmed/18378767

Antidepressants: National Institute of Clinical Excellence: National Clinical Guideline Number 192: Antenatal and postnatal mental health – clinical management and service guidance, April 2018. https://www.nice.org.uk/guidance/cg192/evidence/full-guideline-pdf-4840896925

[vi] Carbimazole: Bowman P, Vaidya B. Suspected Spontaneous Reports of Birth Defects in the UK Associated with the Use of Carbimazole and Propylthiouracil in Pregnancy. J Thyroid Res. 2011;2011:235130. https://www.ncbi.nlm.nih.gov/pubmed/21922050

[vii] Dolutegravir: Raesima MM, Ogbuabo CM, Thomas V, Forhan SE, Gokatweng G, Dintwa E, et al. Dolutegravir Use at Conception - Additional Surveillance Data from Botswana. N Engl J Med. 2019 29;381(9):885–7. https://www.ncbi.nlm.nih.gov/pubmed/31329378

[viii] Efavirenz: Mehta UC, van Schalkwyk C, Naidoo P, Ramkissoon A, Mhlongo O, Maharaj NR, et al. Birth outcomes following antiretroviral exposure during pregnancy: Initial results from a pregnancy exposure registry in South Africa. South Afr J HIV Med. 2019;20(1):971. https://www.ncbi.nlm.nih.gov/pubmed/31616571

Efavirenz: Martinez de Tejada B, European Pregnancy and Paediatric HIV Cohort Collaboration Study Group. Birth Defects After Exposure to Efavirenz-Based Antiretroviral Therapy at Conception/First Trimester of Pregnancy: A Multicohort Analysis. J Acquir Immune Defic Syndr. 2019 01;80(3):316–24. https://www.ncbi.nlm.nih.gov/pubmed/30570524

Efavirenz: Zash R, Holmes L, Diseko M, Jacobson DL, Brummel S, Mayondi G, Isaacson A, Davey S, Mabuta J, Mmalane M, Gaolathe T, Essex M, Lockman S, Makhema J, Shapiro RL. Neural-Tube Defects and Antiretroviral Treatment Regimens in Botswana. N Engl J Med. 2019 Aug 29;381(9):827-840. https://www.ncbi.nlm.nih.gov/pubmed/31329379

[ix] Lithium: Munk-Olsen T, Liu X, Viktorin A, Brown HK, Di Florio A, D'Onofrio BM, et al. Maternal and infant outcomes associated with lithium use in pregnancy: an international collaborative meta-analysis of six cohort studies. Lancet Psychiatry. 2018 Aug;5(8):644-652. https://www.ncbi.nlm.nih.gov/pubmed/29929874

[x] Fan H, Gilbert R, O'Callaghan F, Li L. Associations between macrolide antibiotics prescribing during pregnancy and adverse child outcomes in the UK: population based cohort study. BMJ. 2020 Feb 19;368:m331. https://www.ncbi.nlm.nih.gov/pubmed/32075790

	this study (93%) were to erythromycin, but a class effect cannot be ruled out. Macrolides should only be prescribed in pregnancy when clearly indicated.	
Methotrexate	Pregnancy loss, growth restriction, microcephaly, intellectual disability.	*III*[xi]
Contraceptive agents and sex steroids (progestin)	There is no risk for congenital defects if contraceptive agents were used inadvertently during the first trimester. Very high doses of androgen hormone-derived progestin may produce masculinisation if used before 13 weeks of pregnancy.	*II*[xii]
Prednisone	Prednisone does not represent a major teratogenic risk in humans at therapeutic doses, but there is an increased risk (about 3-fold) for cleft palate.	*II*[xiii]
Retinoids	Oral formulation is associated with increased risk of CNS, cardioaortic, ear, and clefting defects. Topical administration is very unlikely to have teratogenic potential because teratogenic serum levels cannot be attained by topical exposure to retinoids.	*III*[xiv]
Tetracyclines (e.g. docycycline)	Produces bone and teeth staining; it does not increase the risk of any malformations but should not be used during pregnancy.	*III*[xv]
Warfarin	Early exposure during pregnancy can result in nasal hypoplasia, intrauterine growth restriction and miscarriage. CNS malformations can occur in late pregnancy exposure because of bleeding. In women with new generation prosthetic heart valves taking warfarin daily at a dose of ≤5mg, the risk of serious teratogenesis is small and warfarin may be safely continued in the first trimester being discontinued prior to delivery to avoid intracranial bleeding in the newborn (substituted with heparin).	*II*[xvi]

ACE-inhibitor: angiotensin-converting enzyme inhibitor; ARB: angiotensin receptor blocker; LoE: level of evidence; DS-TB: drug-sensitive tuberculosis; RHZE: rifampicin/isoniazid/pyrazinamide/ethambutol; CNS: central nervous system

[xi] Methotrexate: Kozlowski RD, Steinbrunner JV, MacKenzie AH, Clough JD, Wilke WS, Segal AM. Outcome of first-trimester exposure to low-dose methotrexate in eight patients with rheumatic disease. Am J Med. 1990 Jun;88(6):589–92. https://www.ncbi.nlm.nih.gov/pubmed/2189302

[xii] Contraceptive agents and sex steroids (progesterone): Raman-Wilms L, Tseng AL, Wighardt S, Einarson TR, Koren G. Fetal genital effects of first-trimester sex hormone exposure: a meta-analysis. Obstet Gynecol. 1995 Jan;85(1):141–9. https://www.ncbi.nlm.nih.gov/pubmed/7800312

[xiii] Prednisone: Park-Wyllie L, Mazzotta P, Pastuszak A, Moretti ME, Beique L, Hunnisett L, et al. Birth defects after maternal exposure to corticosteroids: prospective cohort study and meta-analysis of epidemiological studies. Teratology. 2000 Dec;62(6):385–92. https://www.ncbi.nlm.nih.gov/pubmed/11091360

[xiv] Retinoids: Heckel S, Favre R, Weber P, Dellenbach P. [Teratogenicity of retinoids. A case and review of the literature]. J Gynecol Obstet Biol Reprod (Paris). 1993;22(1):43-7.https://www.ncbi.nlm.nih.gov/pubmed/8463566
Retinoids: Jick SS, Terris BZ, Jick H. First trimester topical tretinoin and congenital disorders. Lancet. 1993 May 8;341(8854):1181–2. https://www.ncbi.nlm.nih.gov/pubmed/8098078

[xv] Tetracycline (e.g. docycycline): Wormser GP, Wormser RP, Strle F, Myers R, Cunha BA. How safe is doxycycline for young children or for pregnant or breastfeeding women? Diagn Microbiol Infect Dis. 2019 Mar;93(3):238–42. https://www.ncbi.nlm.nih.gov/pubmed/30442509

[xvi] Warfarin: Steinberg ZL, Dominguez-Islas CP, Otto CM, Stout KK, Krieger EV. Maternal and Fetal Outcomes of Anticoagulation in Pregnant Women With Mechanical Heart Valves. J Am Coll Cardiol. 2017 Jun 6;69(22):2681–91. https://www.ncbi.nlm.nih.gov/pubmed/28571631

EXTEMPORANEOUS COMPOUNDING

Compounding is the process where a pharmacist or other registered person prepares, mixes, combines, packages or labels a medicine for an individual patient.

Medicines compounded, or prepared "extemporaneously", are unlicensed medicines and not subject to Medicines Regulatory Authority oversight. Thus, assumptions cannot be made regarding quality and stability of these compounded products relative to licensed medicines.

In terms of Section 22C(5) of the Medicines and Related Substances Act, 1965 (Act No. 101 of 1965), "*No person shall compound or dispense a medicine unless he or she is authorised thereto in terms of the Pharmacy Act, 1974, is a veterinarian or is the holder of a licence as contemplated in subsection (1) (a)*." This license may be granted by the Director-General to a medical practitioner, dentist, practitioner, veterinarian, nurse or other person registered under the Health Professions Act, 1974 (Act No. 56 of 1974).

Pharmacists or other registered persons should only engage in extemporaneous preparation when all routes of timely procurement have been exhausted (medicine cannot be sourced locally or globally; suitable therapeutic alternatives are not available or the medicine is not available from an authorised specialised compounding facility), or if the appropriate formulation or strength of the medicine is no readily available.

Extemporaneous preparations should be compounded by a pharmacist or other registered person in accordance with the Medicines and Related Substances Act, 1965 (Act No. 101 of 1965), as amended (adhering to minimum standards relating to premises, facilities and equipment) and at a facility that is licenced according to the Pharmacy Act.

Section 3 of the General Regulations to the Medicines and Related Substances Act, 2017, provides the conditions for compounding a medicine. In terms of Section 3(1) of the Regulations:
"*A pharmacist or other person licensed in terms of section 22C(1)(a) of the Act to compound a medicine for sale in terms of section 14(4) of the Act, shall only compound a quantity that is intended to be used by a patient for no more than 30 consecutive days from the date of compounding: Provided that the date of compounding and the statement "Use within 30 days" are clearly indicated on the label*."

Standard operating procedures will assist to minimise risk regarding calculation errors, inappropriate validation of the preparation, microbial contamination, stability and storage of the compounded product, labelling errors, patient

acceptability and the health and safety of personnel involved in compounding – appropriately aligned with Good Pharmacy Practice regulations.

Labelling should contain batch number, date of preparation, expiry date, the statement “Use within 30 days”, and all relevant labelling specific to the preparation. Relevant record-keeping should be maintained.

Standardised formulas have been provided for the following essential medicines that have supply constraints:

MORPHINE, ORAL SOLUTION FORMULATION GUIDE

Different concentrations of morphine can be compounded to make the oral solution. However, it is recommended that a standard concentration (mg/mL) is used per ward/facility to prevent dosing errors. The following standard concentrations should be used:

- 1 mg/mL
- 5 mg/mL
- 10 mg/mL

Lower concentrations (e.g., 1mg/mL) are used for children and frail care patients where lower doses are usually required.

Dosing for adult patients is generally commenced using concentrations of 5mg/mL or 10mg/mL.

Higher strengths (20mg/mL) may be required in patients with complex pain (e.g. oncology centres and specialist care, opioid tolerant patients).

The volume compounded is dependent on individual patient requirements. Any remaining unused solution must be discarded 30 days from the day of compounding, in keeping with legislation and the expected stability of oral morphine solutions. Therefore, in order to prevent wastage, compound a volume in line with expected usage in a 30-day period. Compounding is usually done for individual patients, but can be done in anticipation of demand, with due regard to the limited stability of oral morphine solutions. Large volumes cannot be prepared for bulk stock and kept in stock awaiting prescriptions. The same approach should be applied to stock prepared for use on hospital wards.

Tables 1 and 2 show the amount (in grams) of morphine hydrochloride/sulphate required to make 100 mL and 500 mL morphine oral solutions, respectively, at concentrations of 1 mg/mL, 5 mg/mL or 10 mg/mL, using nipastat 0.15% solution (procured commercially as a premade solution) as diluent. Varying volumes of nipastat 0.15% are combined with each fixed amount of morphine powder, in order to produce the final volume required.

Table 1: Amount (in grams) of morphine hydrochloride/sulphate required to make a 100 mL oral morphine solution at concentrations of 1 mg/mL, 5 mg/mL or 10 mg/mL

Formula:

Final morphine concentration	**1 mg/mL**	**5 mg/mL**	**10 mg/mL**
Morphine hydrochloride/sulphate	**0.1 g**	**0.5 g**	**1 g**
Nipastat 0.15% Solution*, make up to	To 100 mL	To 100 mL	To 100 mL

*Nipastat 0.15% Solution (2.5 L) procured as a pre-made solution contains methylhydroxybenzoate (2.5 g), propylhydroxybenzoate (1.25 g), alcohol 99% (125 mL), purified water to 2.5L.

Table 2: Amount (in grams) of morphine hydrochloride/sulphate required to make a 500mL oral morphine solution at concentrations of 1 mg/mL, 5 mg/mL or 10 mg/mL

Formula:

Final morphine concentration	**1 mg/mL**	**5 mg/mL**	**10 mg/mL**
Morphine hydrochloride/sulphate	**0.5 g**	**2.5 g**	**5 g**
Nipastat 0.15% Solution*, make up to	To 500 mL	To 500 mL	To 500 mL

*Nipastat 0.15% Solution (2.5 L) procured as a pre-made solution contains methylhydroxybenzoate (2.5 g), propylhydroxybenzoate (1.25 g), alcohol 99% (125 mL), purified water to 2.5 L.

PODOPHYLLIN, TOPICAL SOLUTION

- Podophyllin 20% in compound benzoin tincture BP, 100 mL.

Active ingredient: Podophyllin 200 mg/mL
Dosage form: Topical solution
Excipients: Compound Benzoin Tincture BP

Formula

Podophyllin resin BP	20 g
Compound benzoin tincture BP, add to	100 mL

Preparation

1. Weigh out the podophyllin resin, and place in 100 mL amber glass bottle (previously dried out with a few drops of 70% alcohol).
2. Add compound benzoin tincture to 100 mL and mix well.
3. Decant 10 mL in an amber glass bottle for a treatment course and label appropriately.

Storage: Glass amber bottle, below 25 °C with an expiry date of 6 months.

Quality requirements

Identity: as stated under the section "Declaration", above.
Content of podophyllin: 90–110% of the declared amount, calculated as the pure substance.
Appearance: The solution is clear and almost free of visible particles.
Label: Appropriately labelled for external use only.

POTASSIUM CHLORIDE 1G/5ML ORAL SOLUTION (5L)

Ingredient	Quantity
Potassium Chloride powder	1 kg
Concentrated Chloroform Water AQ	125 mL
Distilled water up to	5 L

(Adapted with permission from Tygerberg Academic Hospital Department Of Pharmaceutical Services)

***Note**: Different volumes can be prepared. Recalculate based on the above proportions.*

Method

1. Weigh off Potassium Chloride powder.
2. Place in a mixing bowl of a small mixer.
3. Heat 2.5 litres distilled water and add to powder.
4. Mix at low speed.
5. Add 1,5 litres of cold water to mixture.
6. Measure off 125ml concentrated Chloroform water and add to mixture.
7. Place in a 5 litre container prepared for the manufacture of Potassium Chloride.
8. Make up to 5 litres with distilled water.
9. Print stickers and fill in packing card.
10. Pack in 100 ml glass amber bottles.

Storage: store in a glass amber bottle for up to 1 month.

Directions for use: Dilute every 5mL with 60mL of fluid (Juice or water)

How to prepare concentrated Chloroform Water B.P (125ml)

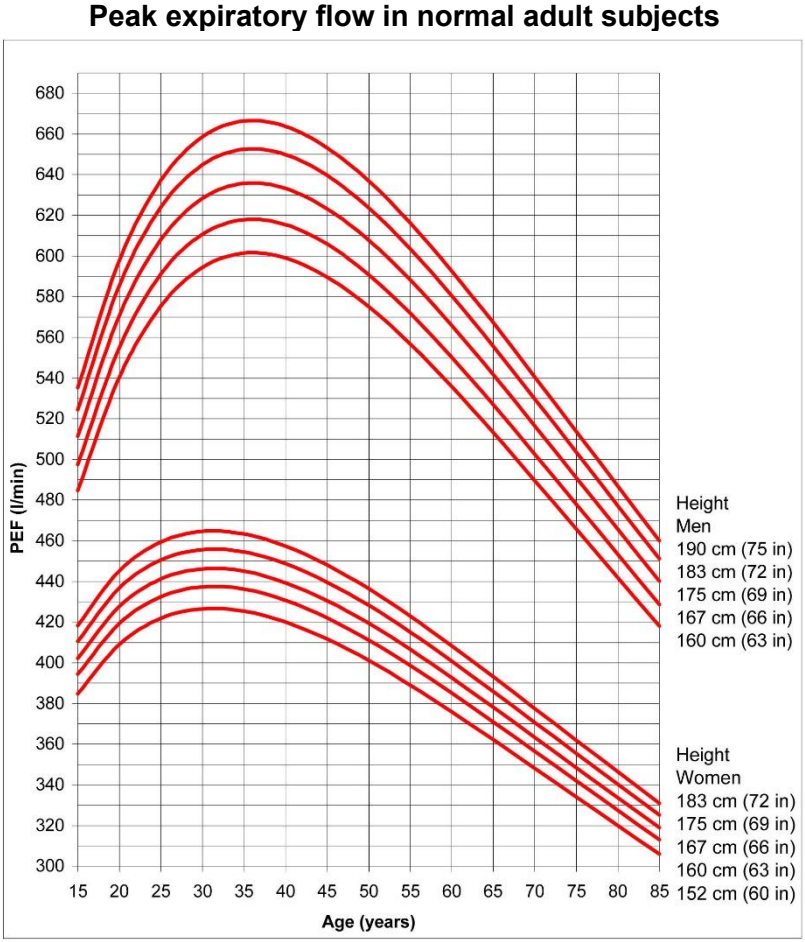
Ingredient	Quantity
Alcohol 96 %	75 mL
Chloroform Liquid	12,5 mL

Distilled water up to	125 mL

Method:

1. Measure alcohol 96 % in glass cylinder and pour into amber glass bottle prepared for the manufacture of Chloroform water.
2. Measure chloroform liquid in a glass cylinder and add to the alcohol. Perform this step expeditiously as Chloroform evaporates.
3. Make up the volume with distilled water.
4. Label bottle with Batch number and date of manufacture.

PEAK EXPIRATORY FLOW RATES



Adapted with permission from Nunn AJ Gregg I, Br Med J 1989:298;1068-70 and Clement Clarke International.

CALCULATING % PREDICTED PEAK FLOW RATE

- Take the best of 3 of the patient's observed peak flow rates (l/min): e.g. 200, 180, 190 performed – so take 200.
- Find the patient's sex, age and height predicted value from the nomogram. e.g. 440 l/min for a woman of age 25 years and height 167 cm
- Divide patient's observed peak flow rate over their predicted peak flow rate: e.g. 200/440 = 0.45
- Multiply by 100: e.g. 0.45 X 100 = 45%

So, in this example, the patient's observed peak flow rate is 45% of their predicted.

CALCULATING BRONCHODILATOR RESPONSIVENESS USING PEAK FLOW IN ADULTS

Perform peak flow testing and select the best of the 3 values to use as the pre-bronchodilator peak flow.

- Administer salbutamol 400 µg using a metered dose inhaler and spacer without a mask.
- Wait 15 minutes before repeating peak flow
- Repeat peak flow testing to obtain a post-bronchodilator peak flow.
- Subtract the pre-bronchodilator reading from the post-bronchodilator reading.
- Divide the difference by the pre-bronchodilator reading.
- Multiply by 100.

For example, a patient with readings that improve from 300 to 400, has reversibility of 33%. Measurements that improve by >20% strongly suggest a diagnosis of asthma. (See Sections 16.1: Asthma, acute and 16.2: Asthma, chronic persistent).

CALCULATING PEAK FLOW VARIABILITY IN CHILDREN AND ADULTS

- Perform peak flow measurements 4 times per day spread over the course of the day.
- Subtract the lowest reading of each day from the highest reading.
- Calculate the mean/average reading by adding all 4 readings from that day and dividing total by 4.
- Calculate PEF variability:

$$\text{PEF variability} = \frac{(\text{Highest PEF} - \text{Lowest PEF})}{\text{Mean PEF}} \times 100.$$

Determine this value on each day over two weeks, and average the results. Excessive diurnal PEF variability defined as >10% in adults and >12% in children strongly supports a diagnosis of asthma.

ASTHMA CONTROL TEST™

This is a validated measure of clinical asthma control that can be completed by the patient (after initial instruction) at each visit to the clinic prior to consultation. A value of ≥19 suggests adequate asthma control.

Online version of the test is accessible at: https://www.asthmacontroltest.com/

Reference: Nathan RA, Sorkness CA, Kosinski M, Schatz M, Li JT, Marcus P, Murray JJ, Pendergraft TB. Development of the asthma control test: a survey for assessing asthma control. J Allergy Clin Immunol. 2004 Jan;113(1):59-65. http://www.ncbi.nlm.nih.gov/pubmed/14713908

INHALER DEVICES

SPACER DEVICES

» Spacers are vital for an adequate therapeutic effect of inhaled therapy.
» Spacer devices should be used for all inhaled medications in all age groups to improve efficacy of medicine delivery and limit adverse effects.
» Use a spacer that is appropriate for the patient's age.

	Spacer volume	Valve	Delivery	Technique
Infants <3 years	150–250 mL	Required	Face mask	Deep tidal breathing
Children 3 to 6 years	500 mL	Required	Mouthpiece	Deep tidal breathing
Children >7 and adults	500 mL	Optional	Mouthpiece	Single inhalation and breath-hold

» Inhalation spacer devices enable optimal aerosol delivery.
» Children < 3 years of age should have a spacer with a face mask, while older children and adults should use the spacer with a mouth piece directly.
» Demonstrate the relevant inhaler technique more than once to ensure the correct procedure (see below). *LoE:IVb*[1]

Patient and caregiver education on inhaler and spacer techniques:
» If patients are switched between different types of devices (e.g. from MDI to DPI), patients need to be re-educated on inhaler technique.
» If changing from a DPI to MDI, consider if a spacer is required, and the optimal technique for inhalation.
» Doses may not be equivalent between different inhaler devices – ensure that patients are prescribed the correct dose when switching between devices.

METERED DOSE INHALERS (MDIs)

» A mask attachment must be used with the spacer for children < 3 years of age and be removed as soon as the child is able to use the mouthpiece.

A. Inhalation therapy without a spacer in adults: Single breath inhalation technique

1. Remove the cap from the mouthpiece.
2. Shake the inhaler well.
3. While standing or sitting upright, breathe out as much air as possible.
4. Immediately place the mouth piece of the inhaler between the lips and gently close the lips around it.
5. Start breathing in slowly.

6. Immediately press down the canister of the metered dose inhaler once to release one puff while simultaneously breathing in as deeply as possible.
7. Hold breath for 5 to 10 seconds, if possible.
8. Breathe out slowly through the nose and rest for a few breaths (30–60 seconds).
9. Repeat steps 2–8 for each puff prescribed.
10. Rinse mouth after inhalation of corticosteroids.

LoE:IVb[2]

B. Inhalation therapy with a spacer in adults and older children: Single breath inhalation technique

1. Remove the caps from the inhaler and the spacer.
2. Shake the inhaler well.
3. Insert the mouthpiece of the metered dose inhaler into the back of the spacer.
4. Insert the mouthpiece of the spacer into the mouth and close the lips around the mouthpiece.
5. Exhale fully into the spacer.
6. Start inhalation and immediately press down the canister of the metered dose inhaler once to release one puff into the spacer.
7. Breathe in slowly to full inhalation and hold the breath for 5 to 10 seconds.
8. Breathe out through the nose.
9. Repeat steps 2–8 for each puff prescribed, waiting at least 30 seconds between puffs.
10. Rinse mouth after inhalation of corticosteroids.

C. Inhalation therapy with the spacer alone in younger children or in adolescent and adults unable to do single inhalation: Deep tidal breathing technique

1. Remove the caps from the inhaler and the spacer.
2. Shake the inhaler well.
3. Insert the mouthpiece of the spacer into the mouth and close the lips around the mouthpiece.
4. Press down the canister of the metered dose inhaler once to release one puff into the spacer.
5. Breathe slowly and deeply in and out of the spacer continuously for at least 6 breaths
6. If breathing through the nose as well as the mouth, pinch the nose gently while breathing from the spacer.

D. Inhalation therapy with a spacer and mask for infants and children < 3 years:

1. Remove the caps from the inhaler and the spacer.
2. Infants may be preferably placed on the caregiver's lap or alternatively laid on a bed while administering the medication.
3. Shake the inhaler well.
4. Apply the mask to the face, ensuring that the mouth and nose are well covered.

5. With the mask held firmly onto the face, press down the canister of the metered dose inhaler once to release one puff into the spacer.
6. Keep the mask in place for at least six breaths, then remove.
7. Repeat steps 3–6 for each puff prescribed, waiting at least 30 seconds between puffs.

DRY POWDER INHALERS (DPIs)

E. Inhalation therapy with a dry powder inhaler (DPI) for adults and children over 6 years of age:

1. There is no need to shake a DPI.
2. Open, twist or click the device to load the medication dose.
3. Stand or sit up straight and breathe out completely (away from the device, not into the mouthpiece).
4. Immediately place the mouthpiece into the mouth, close lips tightly around it and breathe in quickly and forcefully to full inhalation.
5. Remove the DPI from the mouth, hold breath for 5-10 seconds, then exhale slowly.
6. Optimise positioning and repeat steps 2–5 for each puff prescribed, waiting at least 30 seconds between puffs.
7. Rinse mouth with water after inhalation of corticosteroids.

NEBULISERS

The guidance below is tailored to the use of jet nebulisers which are primarily used in the public sector.

1. Ensure the nebuliser cup is filled sufficiently to allow effective nebulisation (approx. 4L minimum volume). Volume must be more than the equipment dead space to be sufficient. The dead space in a nebuliser refers to the volume of the nebulizer chamber and tubing that remains filled with medication after treatment. This volume is not delivered to the patient and can vary depending on the nebulizer design. Typical dead space volumes in jet nebulizers is 2-3 mL.
2. Hold the nebuliser upright.
3. Select a flow rate of oxygen of 6 to 8 L/min for jet nebulisers.
4. Use a mouthpiece rather than a facemask in adults and in any child able to hold a mouthpiece between their lips and breathe via their mouths.
   Better medication delivery: The T-piece allows for more direct delivery of medication to the lungs, reduced medication loss, improved patient comfort, enhanced cooperation, reduced risk of skin irritation and easier observation of the patient's mouth and nose.

5. Place the mouthpiece in the patient's mouth. Advise the patient to keep their lips firmly around the mouthpiece. If using a facemask, place it over the mouth and nose.
6. Ensure patient is calm and relaxed.
7. Advise patient to breathe slowly and deeply through the mouth as far in and as far out as possible until all the medication is used.

The following should be avoided when using nebulisers:

» Rapid or forceful inhalation (including crying)
» Nebulising whilst sleeping
» Using a facemask when a mouthpiece is possible
» A loose-fitting facemask or placing the nebuliser near a child's nose and mouth rather than securing a facemask

LoE:IVb[3]

[1] Spacers: Vincken W, Levy ML, Scullion J, Usmani OS, Dekhuijzen PNR, Corrigan CJ. Spacer devices for inhaled therapy: why use them, and how? ERJ Open Res. 2018 Jun 18;4(2):00065-2018. doi: 10.1183/23120541.00065-2018. PMID: 29928649; PMCID: PMC6004521.
Berlinski A. Pediatric Aerosol Therapy. Respir Care. 2017 Jun;62(6):662-677. doi: 10.4187/respcare.05298. PMID: 28546371.
Patient education: Inhaler techniques in adults (Beyond the Basics) . https://www.uptodate.com/contents/inhaler-techniques-in-adults-beyond-the-basics/print
[2] Optimal aerosol delivery: Levin ME. Optimal aerosol delivery. Current Allergy & Clinical Immunology. 2011; 24(1):27-30
Rubin BK Fink JB. Optimizing aerosol delivery by pressurized metered-dose inhalers. Respir Care 2005; 50 (9): 1191-1200.
Devadason SG. Recent advances in aerosol therapy for children with asthma. J Aerosol Med. 2006 Spring;19(1):61-6. doi: 10.1089/jam.2006.19.61. PMID: 16551216.
Everard ML, Clark AR, Milner AD. Drug delivery from holding chambers with attached facemask. Archives of Disease in Childhood. 1992 May;67(5):580-585. DOI: 10.1136/adc.67.5.580. PMID: 1599292; PMCID: PMC1793709.
Vincken W, Levy ML, Scullion J, Usmani OS, Dekhuijzen PNR, Corrigan CJ. Spacer devices for inhaled therapy: why use them, and how? ERJ Open Res. 2018 Jun 18;4(2):00065-2018. doi: 10.1183/23120541.00065-2018. PMID: 29928649; PMCID: PMC6004521.
Esposito-Festen JE, Ates B, van Vliet FJ, Verbraak AF, de Jongste JC, Tiddens HA. Effect of a facemask leak on aerosol delivery from a pMDI-spacer system. J Aerosol Med. 2004 Spring;17(1):1-6. doi: 10.1089/089426804322994406. PMID: 15120007.
[3] Optimal aerosol delivery: Levin ME. Optimal aerosol delivery. Current Allergy & Clinical Immunology. 2011; 24(1):27-30

NON-LABORATORY BASED RISK SCREENING

BMI-BASED RISK ASSESSMENT

» Measure body mass index (BMI): BMI=weight (kg)/[height (m) x height (m)]

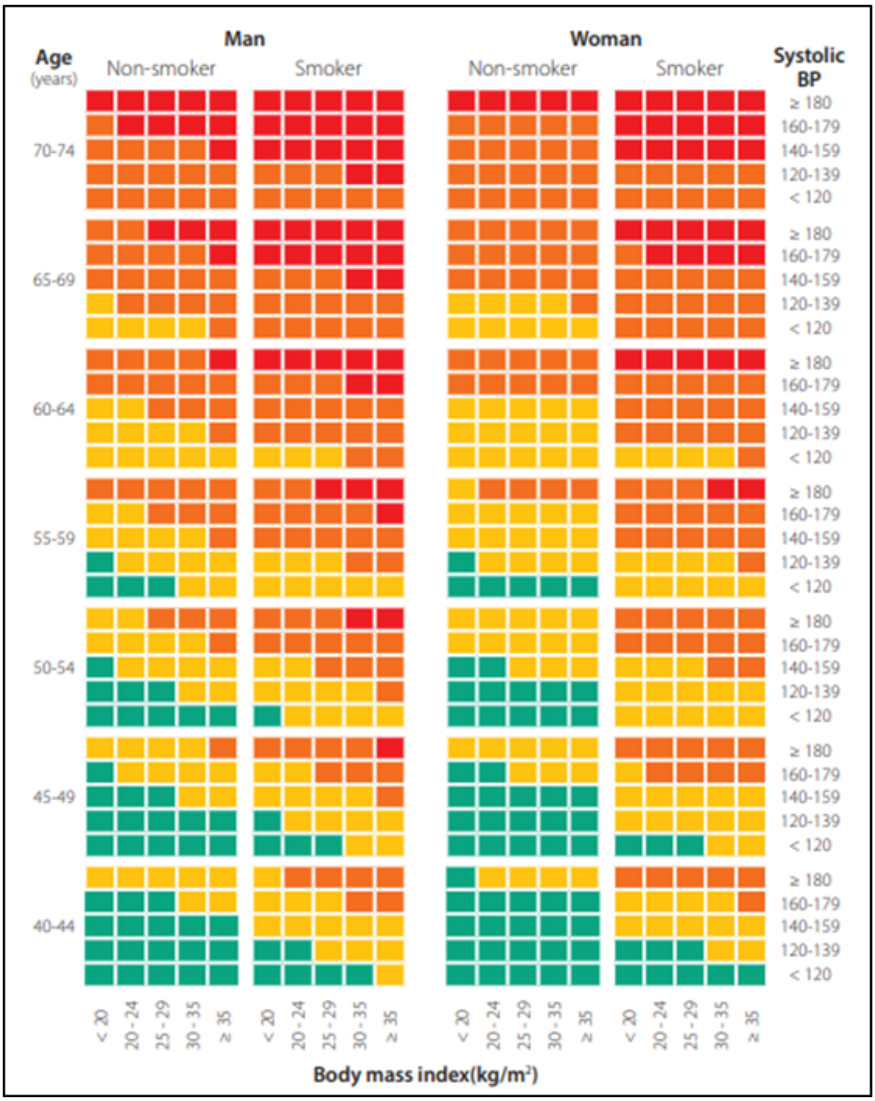
» Measure blood pressure. *LoE:IIIb*[1]

» Calculate 10-year risk of a cardiovascular event using the BMI-based CVD risk tool below.

- Use the patient's sex, age, BMI, systolic BP and smoking status to work out what colour block they fall into
- Explain to the patient what his/her risk of heart attack or stroke might be over the next 10 years

Colour code	CVD risk
	CVD risk < 5%: there is less than a 1 in 20 chance of a heart attack or stroke over the next 10 years
	CVD risk 5-10%: there is between 1 in 10 and 1 in 20 chance of a heart attack or stroke over the next 10 years
	CVD risk 10-20%: there is between 1 in 5 and 1 in 10 chance of a heart attack or stroke over the next 10 years
	CVD risk > 20%: there is more than a 1 in 5 chance of a heart attack or stroke over the next 10 years

» Manage the risk as recommended in Section 4.1 Prevention of heart disease and atherosclerosis.



BMI-based risk assessment

Adopted with permission from the Knowledge Translation Unit and authors of the Adult Primary Care guideline (2023). This tool is based on the WHO cardiovascular disease non-laboratory-based Southern Sub-Saharan Africa. From: HEARTS technical package for cardiovascular disease management in primary healthcare risk based CVD management. World Health Organisation, Geneva, 2020.

LABORATORY BASED RISK SCREENING

FRAMINGHAM RISK SCORE (CHOLESTEROL-BASED)

» To derive the absolute risk as a percentage of patients who will have a cardiovascular event (i.e. death, myocardial infarction or stroke) over 10 years, add the points for each risk category (Section A). The risk associated with the total points is then derived from Section B.

» Calculation of CVD risk using the table:

- A risk of MI > 20% in 10 years equates to ≥ 15 points for men, and ≥ 18 points for women. It is important to score each patient individually, as there are many combinations of risk factors that can add up to those total points.
- For example:

  A male patient > 60 yrs old with systolic BP > 140 mmHg on treatment would score:
  - 11 points for his sex and age
  - 4 points for his on-treatment BP
  - Total: 15 points

  A male patient > 50 yrs old with systolic BP > 130 mmHg on treatment who is a smoker would score:
  - 8 points for his sex and age
  - 3 points for his on-treatment BP
  - 4 points for his smoking status
  - Total: 15 points

  A female patient > 70 yrs old with systolic BP > 160 mmHg on treatment would score:
  - 11 points for her sex and age
  - 7 points for her on-treatment BP
  - Total: 18 points

Calculation of risk of developing cardiovascular events over 10 years (in the absence of cardiovascular disease or genetic disorders such as familial hypercholesterolaemia)

SECTION A

Age (years)	**MEN**	**WOMEN**
30–34	0	0
35–39	2	2
40–44	5	4
45–49	6	5
50–54	8	7
55–59	10	8
60–64	11	9
65–69	12	10
70–74	14	11
75–79	15	12

Total cholesterol (mmol/L)	**MEN**	**WOMEN**
<4.1	0	0
4.1–5.19	1	1
5.2 – 6.19	2	3
6.2–7.2	3	4
>7.2	4	5

HDL cholesterol (mmol/L)	**MEN**	**WOMEN**
>1.5	–2	–2
1.3–1.49	–1	–1
1.2–1.29	0	0
0.9–1.119	1	1
<0.9	2	2

	MEN	**WOMEN**
Smoker	4	3
Diabetic*	3	4

*Type 2 diabetics > 40 years of age qualify for statin therapy irrespective of risk score.

	MEN		**WOMEN**	
Systolic BP (mmHg)	Untreated	Treated	Untreated	Treated
<120	–2	0	–3	–1
120–129	0	2	0	2
130–139	1	3	1	3
140–149	2	4	2	5
150–159	2	4	4	6
≥160	3	5	5	7

SECTION B

Total points

MEN	10-year risk %	WOMEN	10-year risk %
≤–3	<1	≤–2	<1
–2	1.1	–1	1.0
–1	1.4	0	1.2
0	1.6	1	1.5
1	1.9	2	1.7
2	2.3	3	2.0
3	2.8	4	2.4
4	3.3	5	2.8
5	3.9	6	3.3
6	4.7	7	3.9
7	5.6	8	4.5
8	6.7	9	5.3
9	7.9	10	6.3
10	9.4	11	7.3
11	11.2	12	8.6
12	13.2	13	10.0
13	15.6	14	11.7
14	18.4	15	13.7
15	21.6	16	15.9
16	25.3	17	18.5
17	29.4	18	21.5
≥18	>30	19	24.8

Framingham risk score assessment

[1] BMI-based CVD risk assessment: D'Agostino RB Sr, Vasan RS, Pencina MJ, Wolf PA, Cobain M, Massaro JM, Kannel WB. General cardiovascular risk profile for use in primary care: the Framingham Heart Study. Circulation. 2008 Feb 12;117(6):743-53. https://www.ncbi.nlm.nih.gov/pubmed/18212285

GUIDELINES FOR THE MOTIVATION OF A NEW MEDICINE ON THE NATIONAL ESSENTIAL MEDICINES LIST

Section 1: Medication details

» Generic name
A fundamental principle of the Essential Drug Programme is that of generic prescribing. Most clinical trails are conducted using the generic name.

» Proposed indication
There will usually be many registered indications for the medication. However, this section should be limited to the main indication which is supported by the evidence provided in section 2.

» Prevalence of the condition in South Africa
This information is not always readily available. However, it is an important consideration in the review of a proposed essential medicine.

» Prescriber level
Here the proposed prescriber level should be included. If more than one level is proposed each relevant box should be ticked.

Section 2: Evidence and motivation

» Estimated benefit
- Effect measure: this is the clinical outcome that was reported in the clinical trial such as BP, FEV, CD_4, VL etc.
- Risk benefit: this should reported in the clinical trial and, in most cases, includes the 95% confidence level (95% CI). Absolute risk reduction, also termed risk difference, is the difference between the absolute risk of an event in the intervention group and the absolute risk in the control group.
- Number Need to Treat (NNT): gives the number of patients who need to be treated for a certain period of time to prevent one event. It is the reciprocal of the absolute risk or can be calculated using the formula on page xxxv.

Calculations

	Bad outcome	Good outcome	Total patients
Intervention group	*a*	*c*	*a + c*
Control group	*b*	*d*	*b + d*

Measure	Equation
Absolute risk:	[b/(b+d)] – [a/(a+c)]
Number needed to treat	$\frac{1}{[b/(b+d)] - [a/(a+c)]}$
Relative risk	[a/(a+c)] ÷ [b/(b+d)]
Odds ratio	$\frac{[a/(a+c)] \div [c/(a+c)]}{[b/(b+d)] \div [d/(b+d)]} = (a/c) \div (b/d)$

Reference - Aust Prescr 2008;31:12–16)

» Motivating information (**Level of evidence based on the SORT system**)
  – The National Essential Medicines List Committee has endorsed the adoption of the SORT system for categorising levels of evidence. This system[1] contains only three levels:

Level I	Good quality evidence	Systematic review of RCTs with consistent findings High quality individual RCT
Level II	Limited quality patient oriented evidence	Systematic review of lower quality studies or studies with inconsistent findings Low quality clinical trial Cohort studies Case-control studies
Level III	Other	Consensus guidelines, extrapolations from bench research, usual practice, opinion, disease-oriented evidence (intermediate or physiologic outcomes only), or case series

A: Newer product: for most newer products, level I evidence such as high quality systematic reviews or peer-reviewed high quality randomised controlled trials should be identified and referenced in the space provided.

[1] Ebell MH, Siwek J, Weiss BD, et al. Strength of recommendation taxonomy (SORT): a patient-centered approach to grading evidence in the medical literature. Am Fam Physician. 2004;69:550-6.

B: Older products: many of these products were developed prior to the wide use of randomised controlled trials. However, there may be level I evidence where the product was used as the control arm for a newer product. If no level I evidence can be identified, then level II data from poorer quality controlled trials or high quality observational studies should be referenced in the space provided.

» Cost considerations
  - Where a published reference supporting the review of cost is available comments should be made regarding its applicability to the South African public sector environment.
  - Possible unpublished information that can be included:
    - Cost per daily dose or course of therapy – for long term or chronic therapy such as hypertension the usual daily dose should be calculated (Dose x number of times a day) and converted into the number of dosing units e.g. tablets. This is then used to calculate the cost per day. For medications used in a course of therapy such as antibiotics this is then multiplied by the number of days in the course of therapy.
    - Cost minimisation is used where there is evidence to support equivalence and aims to identify the least costly treatment by identifying all the relevant costs associated with the treatment.
    - Cost-effectiveness analysis is used to compare treatment alternatives that differ in the degree of success in terms of the therapeutic or clinical outcome. By calculating a summary measurement of efficiency (a cost-effectiveness ratio), alternatives with different costs, efficacy rates, and safety rates can be fairly compared along a level playing field.

Where any of these have been performed tick the relevant block and send as an attachment with all the calculations. If possible, the spread sheet should be supplied electronically.

Section 3: Motivator's Details

The receipt of all submission will be acknowledged. In addition, all decisions with supporting arguments will be communicated where appropriate. This section therefore forms a vital link between the motivator and the decision making process.

Note: The evidence for decisions informing the selection of a medicine is cited in the STGs, with the respective level of evidence. For example, the following abbreviation is used to describe good quality RCT evidence: '*LoE: I*'.
Where possible, hyperlinks are provided for cited evidence.
The rationale for decision-making may be sourced from the relevant medicine reviews, costing analysis reports or NEMLC reports which are accessible from the National Department of Health website at: https://www.health.gov.za/nhi-edp-stgs-eml/

DEPARTMENT OF HEALTH
Republic of South Africa

Motivation form for the inclusion of a new medication on the National Essential Medicines List

Section 1: Medication details			
Generic name (or International Non-proprietary Name):			
Proposed indication:			
Prevalence of condition (based on epidemiological data, if any):			
Prescriber level			
Primary Health Care 1	Medical Officer 2	Specialist 3	Designated Specialist 4

Section 2: Evidence and motivation			
2.1 Estimated benefit			
Effect measure			
Risk difference (95% CI)			
NNT			
2.2: Motivating information (Level of evidence based on the SORT system)			
A. Newer product: High quality systematic reviews or peer-reviewed high quality randomised controlled trials (Level I)			
Author	Title		Journal ref
B. Older product with weaker evidence base: Poorer quality controlled trials or high quality observational studies (Level II)			
Author	Title		Journal ref
2.3: Cost-considerations			
Have you worked up the cost?	YES		NO
	Daily cost	Cost minimisation	Cost-effectiveness analysis
Other relevant cost information if available:			
Author	Title		Journal ref
2.4: Additional motivating comments.			

Section 3: Motivator's Details	
Name:	**Date submitted:**
Qualification:	**Registration number:**
PTC motivation: Y/N	**PTC Details:**
PTC Chair:	**PTC Chair signature:**

GUIDELINES FOR ADVERSE DRUG REACTION REPORTING

National Pharmacovigilance Programme

The South African Health Products Regulatory Authority (SAHPRA) has a responsibility to ensure the safety, efficacy and quality of all medicines used by the South African public. The National Pharmacovigilance Programme is coordinated by the SAHPRA and has a dedicated Unit, Pharmacovigilance, at the SAHPRA head office, in Pretoria, which monitors the safety of all registered medicines in South Africa.

What is Pharmacovigilance?

Pharmacovigilance is defined as the science and activities concerned with the detection, assessment, understanding and prevention of adverse reactions to medicines (i.e. adverse drug reactions or ADRs). The ultimate goal of this activity is to improve the safe and rational use of medicines, thereby improving patient care and public health.

What is an Adverse Drug Reaction (ADR)?

SAHPRA defines an Adverse Drug Reaction (ADR) as a response to a medicine which is noxious and unintended, including lack of efficacy, and which occurs at any dosage and can also result from overdose, misuse or abuse of a medicine.

Who should report Adverse Drug Reactions?

All health care workers, including doctors, dentists, pharmacists, nurses and other health professionals are encouraged to report all suspected adverse reactions to medicines (including vaccines, X-ray contrast media, traditional and herbal remedies), especially when the reaction is not in the package insert, potentially serious or clinically significant.

According to Regulation 40 of the Medicines and Related Substances Act, 1965 (Act 101 of 1965) as

amended: A healthcare professional /provider, veterinarian or any other person should inform the SAHPRA, in the manner as determined by the Authority, of any:

- suspected ADRs/AEFIs; or
- new or existing safety, quality or effectiveness concerns, occurring as a result of the use of any medicine or scheduled substance

What happens to a report?

All ADR reports are entered into a national ADR database. Each report is evaluated to assess the causal relationship between the event and the medicine. A well-completed adverse drug reaction/product quality form submitted could result in any of the following:

» additional investigations into the use of the medicine in South Africa;
» educational initiatives to improve the safe use of the medicine;
» appropriate package insert changes to include the potential for the reaction, and
» changes in the scheduling or manufacture of the medicine to make it safer.

The purpose of ADR reporting is to reduce the risks associated with the use of medicines and to ultimately improve patient care.

Will reporting have any negative consequences on the health worker or the patient?

An adverse drug reaction report does not constitute an admission of liability or that the health professional contributed to the event in any way. The outcome of a report, together with any important or relevant information relating to the reaction, will be sent back to the reporter as appropriate. The details of a report are stored in a confidential database. The names of the reporter or any other health professionals named on a report and that of the patient will be removed before any details about a specific adverse drug reaction are used or communicated to others. The information is only meant to improve the understanding of the medicines used in the country.

Is the event possibly an ADR?

The following factors should be considered when an adverse drug reaction is suspected:

1. What exactly is the nature of the reaction? (*Describe the reaction as clearly as possible and where possible provide an accurate diagnosis.*)
2. Did the reaction occur within a reasonable time relationship to starting treatment with the suspected medicine? *(Some reactions occur immediately after administration of a medicine while others take time to develop.)*
3. Is the reaction known to occur with the particular medicine as stated in the package insert or other reference? *(If the reaction is not documented in the package insert, it does not mean that the reaction cannot occur with that particular medicine.)*
4. Did the patient recover when the suspected medicine was stopped? *(Some reactions can cause permanent damage, but most reactions are reversible if the medication is stopped.)*
5. Did the patient take the medicine again after the reaction abated (i.e. rechallenge). If so, did the same reaction occur again? *(In most situations it is not possible or ethical to rechallenge the patient with the same medicine. If such information is available or if such a rechallenge is necessary, recurrence of the event is a strong indicator that the medicine may be responsible.)*
6. Can this reaction be explained by other causes (e.g. underlying disease/s; other medicine/s; toxins or foods)? *(It is essential that the patient is thoroughly investigated to decide what the actual cause of any new medical problem is. A medicine-related cause should be considered, when other causes do not explain the patient's condition.)*

What types of reactions should be reported?

The following adverse drug reactions should be reported:

- All ADRs to newly marketed drugs or new medicines added to the EML.
- All serious reactions and interactions
- ADRs that are not clearly stated in the package insert.
- All adverse reactions or poisonings to traditional or herbal remedies

Report even if you are not certain that the medicine caused the event.

What Product Quality Problems should be reported?

The following product quality problems should be reported:

- suspected contamination;
- questionable stability;
- defective components;
- poor packaging or labeling;
- therapeutic failures.

How can ADRs be prevented from occurring?

Some ADRs are unavoidable and cannot be prevented. However, most ADRs can be prevented by following the basic principles of rational use of medicines.

How are adverse drug reactions reported?

An Adverse Drug Reaction/Product Quality Report Form is enclosed in this book and should be completed in as much detail as possible before returning it by fax or post to any of the addresses provided below. Additional forms can be obtained by contacting the SAHPRA at these addresses. Reporting forms may also be accessed via the SAHPRA website: https://www.sahpra.org.za/

1. The CEO OF SAHPRA

South African Health Products Regulatory Authority (SAHPRA), Private Bag X828
Pretoria, 0001
Tel: (012) 5010311; E-mail: adr@sahpra.org.za

2. South African Health Products Regulatory Authority (SAHPRA)

Head Office
Building A, Loftus Park, 402 Kirkness Street
Arcadia, Pretoria, 0001
Tel: (012) 501 0300

Doc Number: GLF-CEM-PV-06A *[Old Doc no. 6.04]*	**ADVERSE DRUG REACTION (ADR)/ PRODUCT QUALITY PROBLEM REPORT FORM** **(PUBLIC AND PRIVATE SECTOR) (Including Herbal Products)**	SAHPRA South African Health Products Regulatory Authority
Revision: 3.0		Effective date: 11 October 2023

See Page 2 for CONSENT CLAUSE, more information regarding reporting of PRODUCT QUALITY PROBLEMS and ADVERSE EVENTS FOR VACCINES

Reporting Health Care Facility/Practice

Building A, Loftus Park **402 Kirkness Street, Arcadia,** **Pretoria** **Tel: (012) 501 0311** **E-mail: adr@sahpra.org.za**	Facility/Practice			
	District		Tel	
	Province		Fax	

Patient Details

Patient Initials		File/Reference Number				Date of Birth/Age			
Sex	☐M ☐F ☐Unk	Race		Weight (kg)		Height (cm)		Pregnant?	☐N ☐Y
Allergies		☐ **Follow up report** **Reference number:** _____						Estimated gestational age at time of reaction	

Suspect Medicine(s) [Medicines suspected to have caused the ADR], Concomitant [Other medicines taken together with the suspect medicine(s)] OR Interacting [Other medicines taken together with the suspect medicine(s)] [Including over the counter and herbal products].

Trade Name [Active Ingredient if Trade Name is unknown]	Medicine role (Please tick the applicable box)	Route	Dose (mg) and Interval	Date Started/ Given	Date Stopped	Reason for use	Batch Number	Expiry Date
	☐ Suspect ☐ Concomitant ☐ Interacting							
	☐ Suspect ☐ Concomitant ☐ Interacting							
	☐ Suspect ☐ Concomitant ☐ Interacting							
	☐ Suspect ☐ Concomitant ☐ Interacting							
	☐ Suspect ☐ Concomitant ☐ Interacting							

Adverse Drug Reaction/Product Quality Problem

Date and time of onset of reaction		Date reaction resolved	

Please describe Adverse Event/Product Quality Problem: (kindly add as much clinical information as possible)

Intervention (Tick all that apply)	**Patient Outcomes** (Tick all that apply)	**ADR seriousness criteria** (Tick all that apply)
☐ No intervention. ☐ Intervention unknown. ☐ Patient counselled/non-medical treatment. ☐ Discontinued suspect drug; **Replaced with**: _____ ☐ Decreased suspect drug dosage; **New Dose**: _____ ☐ Treated ADR – with: _____ ☐ Referred to hospital: **Hospital name**_____ ☐ Other intervention (e.g., dialysis): _____	☐ ADR recovered/resolved. ☐ Recovering/resolving. ☐ Not recovered/not resolved. ☐ Recovered with sequelae. ☐ ADR resolved after suspect medicine was stopped: ☐N ☐Y. ☐ ADR reappeared after restarting suspect drug/similar drug (rechallenge): ☐N ☐Y ☐ Not done ☐ Unknown	☐ Resulted in death. Date of death: _____ ☐ Patient hospitalised or hospitalisation prolonged. ☐ Life threatening. ☐ Impairment/disability. ☐ Congenital anomaly/ birth defect. ☐ Other medically important condition.

Laboratory Results			**Additional Laboratory Results**		
Lab Test	**Test Result**	**Test Date**	**Lab Test**	**Test Result**	**Test Date**

Co-morbidities/Other Medical Condition(s)

Reported by				
Name		E-mail		
Designation	☐Nurse ☐Pharmacist ☐Doctor ☐Other:		Telephone	
Date reported:			Signature	

THIS ADR REPORT IS NOT A CONFIRMATION THAT THE REPORTER OR THE SUSPECT MEDICINE(S) CAUSED THE ADR

ADVICE ABOUT VOLUNTARY REPORTING

Report adverse experiences with:

- medications (medicines and biologicals),
- complementary / alternative medicines (including traditional, herbal remedies, etc).

Please report especially:

- adverse drug reactions to newly marketed products,
- serious reactions and interactions with all products,
- adverse drug reactions which are not clearly reflected in the package insert.

Report Product Quality Problems such as:

- suspected contamination,
- questionable stability,
- defective components,
- poor packaging or labelling,
- therapeutic failures.

Report even if:

- you're not certain the product caused the event,
- you don't have all the details.

Report adverse events experiences with Medical Device via:

- phone: 012 501 0476
- mdvigilance@sahpra.org.za

Report Adverse Events Following Immunisation (AEFI) experienced with vaccines on:

- the dedicated Case Reporting Form accessed from SAHPRA portal: https://www.sahpra.org.za/health-products-vigilance/
- forward the dedicated form to AEFI@health.gov.za
- phone: 0800 02 9999.

Report Product Quality Problems via:

- phone: 0800 204 307

SAHPRA portal: https://www.sahpra.org.za/complaints-relating-to-medicine-and-medical-devices/

Other reporting tools available at SAHPRA include:

Med Safety Application

The Med Safety Application is a mobile application designed for the public and healthcare professionals to report suspected ADRs/adverse event following immunisations (AEFIs). It is the preferred reporting tool by SAHPRA and allows for a seamless electronic submission of ADR/AEFI reports directly from the source into SAHPRA's reporting systems. The app can be downloaded onto a smart mobile phone directly from the SAHPRA website, https://medsafety.sahpra.org.za.
For more reporting channels please visit SAHPRA website, https://www.sahpra.org.za

CONSENT CLAUSE

By the signature above, the reporter hereby provides consent to the processing of personal information provided for the purpose of reporting a suspected adverse reaction. The reporter acknowledges that this information may be used a) to access all medical and clinical records for the purpose of gathering additional information for a clinical meaningful data, when required; b) in the generation of statistics; and c) to make policy decisions relating to safe use of medicines.

SAHPRA's Vigilance unit undertakes to collate the personal information contained in this form and collected during the process of reporting of suspected adverse drug reaction in a manner that adheres to the Protection of Personal Information Act, so that your personal data is processed fairly, lawfully and transparently, adequate, relevant, and limited to what is necessary, processed for specific and legitimate purposes, accurate and kept up to date where necessary, kept in an identifiable form no longer than necessary for the purpose and processed securely . SAHPRA has placed appropriate technical and organisational measures to safeguard your information. The information will not be stored for any longer than is necessary to achieve the purpose for which it was collected, unless the unit has a lawful basis to do so. If the reporter wishes to access and/or rectify their personal information, they may do so by contacting SAHPRA's Vigilance unit at 012 501 0311 or via email: adr@sahpra.org.za.

Confidentiality:

Identities of the reporter and patient will remain strictly confidential.

Your support of the South African Health Products Regulatory Authority's adverse drug reaction monitoring programme is much appreciated. Information supplied by you will contribute to the improvement of medicine safety and therapy in South Africa.

DISEASE NOTIFICATION PROCEDURES

The disease reporting system in South Africa is based on government law (the Health Act, Act No. 61 of 2003), together with regulations on the reporting of specific diseases to the Local, Provincial and/or National Health Department.

Who should notify

The first health care professional to come into contact with a patient presenting with one of the prescribed Notifiable Medical Conditions (NMCs) is required by law to notify. This may include clinic personnel, infection control nurses, other hospital staff or private medical practitioners. In the event of deaths (or cases) in the community, a member of the community is obliged to notify the event.

Which diseases to notify

Currently 33 broad medical conditions are currently notifiable in South Africa (see List of Notifiable Medical Condition). Some conditions (e.g. tuberculosis and viral hepatitis) have been divided into various components, resulting in more than 40 notifiable medical conditions.

Notifiable medical conditions have been sub-divided into two categories according to type of disease:

Category 1 NMC: Requires immediate reporting by the most rapid means available upon clinical or laboratory diagnosis followed by a written or electronic notification to the Department of Health, within 24 hours of diagnosis by health care providers, private health laboratories or public health laboratories.

Any health care professional identifying even a single case of a disease (presumptive or laboratory confirmed) contained in the Category 1 should make an immediate notification directly to the designated local health officer through fax or telephonically as rapidly as possible (within 24 hours). The local health officer must report to the Provincial health officer and/or to the National Department of Health. Where it is applicable, laboratory confirmation should be obtained at the earliest opportunity and also reported to the designated health office. After reporting through a telephone/fax, it is still required of the health care provider to send a complete GW17/5 form to the designated local health authority within five days after telephonic reporting.

Category 2 NMC: Requires reporting through a written or electronic notification to the Department of Health, within 7 days of diagnosis by health care providers, private health laboratories or public health laboratories.

The notification system is based on clinical notifications and, therefore, all suspected cases of a notifiable condition must be notified immediately.

Reporting a Notifiable Disease during an outbreak
During an outbreak of a notifiable disease, report all cases by phone, email or fax. Daily reporting by health facilities should be maintained through an Outbreak Case Line Listing Form as well through the notification form (GW17/5) to the local health authority that must report to the provincial health officials and the National Department of Health.

Priority Reporting of MDR & XDR-TB
Tuberculosis (TB) is one of 33 medical conditions, which is notifiable in terms of the National Health Act (Act 61 of 2003). The Directorate: Epidemiology and Surveillance have instituted a priority reporting for MDR and XDR TB. This means that all health care facilities, public and private, including clinics, hospitals, laboratories, general practitioners and private specialist doctors, are required to report all cases of MDR and XDR TB to the Department of Health within 24 hours.

How to notify
The initial notification of a medical condition is done on a case-based form (*GW 17/5*) with the relevant details by the health personnel e.g., clinic personnel, infection control nurses, other hospital staff, public or private medical practitioners. Initial notification makes tracing as easy as possible, since a disease notification demands action (follow-up) at the peripheral level.
The GW17/5 form makes provision for the notification of cases as well as deaths. Any person contracting a notifiable disease and then dies from the disease should be notified twice: first as a **"CASE"** and then later as a **"DEATH".** This will ensure that when estimating the **"Case Fatality Rate"** (CFR%), all deaths in the numerator are also included in the denominator. Depending on the structural organization of the province, the completed **GW 17/5** forms is sent to the relevant local health authority, district health office or the provincial office.

How to notify
» *Electronically:*
1. Capture the NMC case details onto the NMC electronic system. https://www.nicd.ac.za/nmc-overview/notification-process/

» *Paper-based:*
1. Complete the NMC Case Notification Form. https://www.nicd.ac.za/nmc-overview/notification-forms/
2. Send the NMC Case Notification Form to NMCsurveillanceReport@nicd.ac.za or fax to **086 639 1638**
3. Send a copy to the NMC focal person at Sub-District/District.

Sms/whatsup line (for copy/photograph submissions): 072 621 3805
Email address: NMCsurveillanceReport@nicd.ac.za

List of Notifiable Medical Conditions

Category 1: *Immediate notification (within 24 hours) of diagnosis*
Acute flaccid paralysis
Acute rheumatic fever
Anthrax
Botulism
Cholera
Diphtheria
Food borne disease outbreak*
Haemolytic uraemic syndrome (HUS)
Listeriosis
Malaria
Measles
Meningococcal disease
Pertussis
Plague
Poliomyelitis
Rabies (human)
Respiratory disease caused by a novel respiratory pathogen**
Rift valley fever (human)
Smallpox
Viral haemorrhagic fever diseases***
Yellow fever

Category 2: *Notification within seven days of diagnosis*
Agricultural or stock remedy poisoning
Bilharzia (schistosomiasis)
Brucellosis
Congenital rubella syndrome
Congenital syphilis
Haemophilus influenzae type B
Hepatitis A
Hepatitis B
Hepatitis C
Hepatitis E
Lead poisoning
Legionellosis
Leprosy
Maternal death (pregnancy, childbirth and puerperium)
Mercury poisoning
Soil transmitted helminths
Tetanus
Tuberculosis: pulmonary
Tuberculosis: extra-pulmonary
Tuberculosis: multidrug-resistant (MDR-TB)
Tuberculosis: extensively drug-resistant (XDR-TB)

ABBREVIATIONS

3TC	lamivudine	M	molar
ab	antibody	m2	square metre
ABC	abacavir	MAC	minimum alveolar concentration
ABG	Arterial Blood Gas	MAP	mean arterial pressure
ACE-inhibitor	angiotensin converting enzyme inhibitor	MC	Mucosal candidiasis
ACR	albumin creatinine ratio	mcg	microgram
ACTH	adrenocorticotropic hormone	MCH	mean corpuscular haemoglobin
ADH	antidiuretic hormone	MCPAP	Massachusetts Child Psychiatry Access Project
ADR	adverse drug reaction	MCS	Fluid microscopy and culture
AED	automated external defibrillator	MCV	mean corpuscular volume
AFB	Acid Fast Bacilli	MDEA	3,4-methylenedioxy-N-ethylamphetamine (“Ice”, “Eve”)
Al	Aluminium	MDI	metered dose inhaler
AIDP	acute inflammatory demyelinating polyradiculoneuropathy	MDMA	3,4-methylenedioxymethamphetamine (“Ecstasy”)
AIDS	Acquired Immune Deficiency Syndrome	MDR-TB	multi-drug resistant tuberculosis
AKI	acute kidney injury	MEN2	Multiple endocrine neoplasia type 2
ALP	alkaline phosphatase	MERS	Middle East Respiratory Syndrome
ALT	alanine aminotransferase	MERS-CoV	Middle East Respiratory Syndrome Coronavirus
AMH	anti-mullerian hormone	mg	milligram

AMR	Antimicrobial Resistance	Mg	Magneisum
ANCA	Antineutrophil Cytoplasmic Antibodies	MHCA	Mental Health Care Act No. 17 of 2002
ANF	Atrial Natriuretic Factor	MHCU	mental health care user
aPTT	activated partial thromboplastin time	MI	myocardial infarction
ARB	Angiotensin receptor blocker	MIC	Minimum Inhibitory Concentration
ARDS	Acute respiratory distress syndrome	MIS-C	Multisystem inflammatory syndrome in children
ART	antiretroviral therapy	MIS-A	Multisystem inflammatory syndrome in adults
ASSIST	Alcohol, Smoking, and Substance Involvement Screening Test	mL	millilitre
AST	aspartate aminotransferase	mm3	Cubic millimetre
ATV/r	atazanavir/ritonavir	mmHg	Millimetres mercury
AUB	abnormal uterine bleeding	mmol	millimole
AV	atrioventricular	mMRC	modified medical research council
AZT	zidovudine	mOsm	milliosmole
β-hCG	beta human chorionic gonadotropin	MRI	magnetic resonance imaging
β-blocker	beta-receptor blocker	MRSA	Methicillin resistant *Staphylococcal aureus*
β2-agonist	beta2-receptor blocker	MSU	Mid-stream specimens of urine
BD	bipolar disorder	MTB	*Mycobacterium tuberculosis*
BMI	body mass index	MTP	Massive Transfusion Protocol

BMD	Bone Mineral Density	MU	million units
BP	blood pressure	MVA	manual vacuum aspiration
BPC	British Pharmaceutical Codex	Na	sodium
BPRS	Brief Psychiatric Rating Scale	NAC	N-acetylcysteine
bpm	beats per minute	NaCl	sodium chloride
BSA	body surface area	NaHCO3	Sodium Bicarbonate
BVM	Bag valve mask	NCD	non-communicable disease
Ca	calcium	NDMR	non-depolarising muscle relaxant
CAB (sequence)	circulation airway breathing (sequence)	NEMLC	National Essential Medicines List Committee
CAD	Coronary artery disease	NERD	non-erosive reflux disease
CAM-ICU 7	Standard screening tool for delirium in ICU	NF1	Neurofibromatosis type 1
CCF	congestive cardiac failure	ng	nanogram
CD	Caesarean Delivery	NGO	non-government organisation
CD	crohn's disease	NGT	nasogastric tube
CD4	cluster of differentiation 4 (T-cells)	NHLS	National Health Laboratory Services
CHC	community health centre	NICD	National Institute of Communicable Diseases
CIDP	chronic inflammatory demyelinating polyradiculoneuropathy	NICE	National Institute for Health and Care Excellence
CIN	contrast induced nephrotoxicity	NIV	Non-invasively

CKD	chronic kidney disease	NMA	normetanephrine
CKRT	Continuous kidney replacement therapy	nmol	nanomole
Cl	Chlorine	NNRTI	Non-nucleoside reverse transcriptase inhibitors
cm	centimetre	NPSIRL	National Patient Safety Incident Reporting and Learning
CMV	cytomegalovirus	NRTI	nucleoside reverse transcriptase inhibitor
CNS	cental nervous system	NNT	number needed to treat
C02	Carbon dioxide	NPH insulin	Neutral Protamine Hagedorn insulin
COPD	chronic obstructive pulmonary disease	NRS	numeric rating scale
COVID-19	Coronavirus Disease-19	NSAID(s)	non-steroidal anti-inflammatory drug(s)
CPAP	continuous positive airway pressure	NST	non-stress test
CPR	Cardio-pulmonary resuscitation	NSTEMI	non-ST elevation myocardial infarction
CRE	Carbapenem Enterobacterales	NUD	Non-ulcer dyspepsia
CrAg	cryptococcal antigen	NVP	nevirapine
CrCl	creatinine clearance	NYHA	New York Heart Association (functional classification)
CRP	c-reactive protein	OOWS	objective opioid withdrawal scale
CSF	cerebrospinal fluid	ORS	oral rehydration solution
CSU	Catheter specimens of urine	OI	Opportunistic Infections
CT	computerized tomography	OT	occupational therapy

CTG	cardiotocography	PaCO2	partial pressure of carbon dioxide in arterial blood
CVA	Cerebrovascular Accident	PaO2	partial pressure of oxygen in arterial blood
CVD	cardiovascular disease	PAIR	percutaneous aspiration injection of helminthicidal agent and re-aspiration
CXR	chest x-ray	PANSS	Positive and Negative Syndrome Scale
DBP	diastolic blood pressure	PCA	patient controlled analgesia
DC	direct current	PCI	percutaneous coronary intervention
DILI	drug-induced liver injury	PCO2	Partial Pressure of carbon dioxide
DIC	disseminated intravascular coagulation	PCR	protein creatinine ratio/polymerase chain reaction
dL	decilitre	PCV13	polyvalent conjugated vaccine (13-valent)
DKA	diabetic ketoacidosis	PD	Pharmacodynamic
DMARD	disease-modifying anti-rheumatic drug	PEA	pulseless electrical activity;
DMPA	Depomedroxyprogesterone Acetate	PEEP	Positive End Expiratory Pressure
DNA	deoxyribonucleic acid	PEF	peak expiratory flow
DNAR	Do not attempt resuscitation	PEFR	peak expiratory flow rate
DNR	Do not resuscitate	PEG	polyethylene glycol
DOACs	Direct Oral Anticoagulants	PEG (scale)	pain, enjoyment and general activity (scale)
DTG	dolutegravir	PEP	post exposure prophylaxis
DU	duodenal ulcer	pH	acidity (partial pressure of hydrogen)
DUDIT	Drug Use Disorders Identification Test	PHC	primary health care
DVT	deep venous thrombosis	PI	protease inhibitor

ECG	electrocardiogram	PID	pelvic inflammatory disease
ECT	electroconvulsive therapy	PK	Pharmacokinetic
EEG	electroencephalogram	PLHIV	people living with HIV
EFV	efavirenz	PO	Oral route
EFW	estimated fetal weight	PO4	phosphate
e.g.	example	PONV	postoperative nausea and vomiting
eFAST	Extended Focused Assessment using Sonography in Trauma	POWA	People Opposing Women Abuse
eGFR	estimated Glomerular Filtration Rate	PPE	Personal Protective Equipment
ELISA	enzyme-linked immunosorbent assay	PPG	post prandial plasma glucose
E or EMB	ethambutol	PPH	post-partum haemorrhage
EML	essential medicines list	PPI	proton pump inhibitor
EMS	Emergency Medical Services	PPROM	preterm prelabour rupture of membranes
EOL	End of Life	PrEP	Pre-exposure prophylaxis
EPI	expanded programme on immunisation	PROM	prelabour rupture of membranes at term
EPO	erythropoietin	PPS23	pneumococcal polysaccharide vaccine (23-valent)
ESAs	erythropoietin stimulating agents	PS	Pressure support
ESKD	End stage renal disease	PSI	Patient Safety Incidents
ESR	erythrocyte sedimentation rate	PT	Prothrombin time

ET	Endotracheal Tube	PTH	parathyroid hormone
FAMSA	Families South Africa	PTL	preterm labour
FBC	full blood count	PTSD	Post-Traumatic Stress Disorder
FDC	fixed dose combination	PTT	prolonged partial thromboplastin time
FDP	Freeze dried Plasma	PV	per vagina (vaginal route)
FE	Iron	PVC	Polyvinyl Chloride
FEV1	forced expiratory volume in 1 second	PZA or Z	pyrazinamide
FFP	fresh frozen plasma	RA	rheumatoid arthritis
FFP	Filtering facepiece	RAAS	Renin-angiotensin-aldosterone system
FH	familial hyperlipidaemia	RASS	Richmond agitation sedation scale
FiO2	fraction of inspired oxygen	R or RIF	rifampicin
fL	Femtoliters	RBC	red blood cell
FPG	fasting plasma glucose	RF	Rheumatoid Factor
FSH	follicle stimulating hormone	Rh	Rhesus
FTA-ABS	fluorescent treponemal antibody absorption	RH	rifampicin/isoniazid combination
FTC	emtricitabine	RHZE	rifampicin/isoniazid/pyrazinamide/ethambutol combination
FVC	forced vital capacity	RPR	rapid plasma reagin
g	gram	RR	Respiratory Rate
G6PD	glucose-6-phosphate dehydrogenase	RRT	renal replacement therapy
GABA	Gamma-Aminobutyric Acid	RR-TB	Rifampicin resistant tuberculosis

GCS	Glasgow Coma Scale	RSTI	repeated supratherapeutic ingestion
GDM	gestational diabetes mellitus	ROSC	Return of spontaneous circulation
GGT	gamma-glutamyl transferase	RUT	rapid urease test
GH	Growth Hormone	SABA	short-acting beta2 agonist
GI(T)	gastrointestinal (tract)	SADAG	South African Depression and Anxiety Group
GORD	gastro-oesophageal reflux disease	SAFMH	South Africa Federation for Mental Health
GTN	Glyceryl Trinitrate	SAH	Subarachnoid hemorrhage
GU	gastric ulcer	SAMF	South African Medicine Formulary
H or INH	isoniazid	SANC	South African Nursing Council
Ham-D	Hamilton Depression Rating Scale	SANCA	South African National Council on Alcoholism and Drug Dependence
HAP	hospital-acquired pneumonia	SAPS	South African Police Services
Hb	haemoglobin	SAS	Symptom Assessment Scale
HbA1c	haemoglobin A1c	SAVP	South African Vaccine Producers
HBeAg	hepatitis B e antigen	SBGM	self-blood glucose monitoring
HBIG	hepatits B immunoglobulin	SBP	systolic blood pressure
HbS	sickle haemoglobin	SC	subcutaneous
HBsAb	hepatitis B surface antibody	SCD	Sickle Cell Disease
HBsAg	hepatitis B surface antigen	SIADH	syndrome of inappropriate antidiuretic hormone (SIADH)
HbSS	sickle cell haemoglobin	SJS	Stevens-Johnson Syndrome

HBV	hepatitis B virus	SL	sublingual
HCl	hydrochloric acid	SLE	systemic lupus erythematosus
HCO3	bicarbonate	SLED	Sustained low efficiency dialysis
HCG	Human Chorionic Gonadotropin	SOFA	Sequential Organ Failure Assessment
HCV	hepatitis C virus	SPEP	serum protein electrophoresis
HCW	healthcare workers	SPICT-SA	Supportive and Palliative Care Indicators Tool for South Africa
HCTZ	hydrochlorothiazide	SSRI	selective serotonin re-uptake inhibitor
HDL	high density lipoprtein	STEMI	ST elevation myocardial infarction
HE	hepatic encephalopathy	STD/ STI	sexually transmitted disease/infection
HELLP syndrome	haemolysis, elevated liver enzymes, low platelet count syndrome	STG	standard treatment guideline
Hep B	hepatitis B	SVC	superior vena cava
HHS	hyperglycaemic hyperosmolar syndrome	T3	triiodothyonine
HIET	High-dose insulin euglycemic therapy	T4	thyroxine
HIT	Heparin Induced Thrombocytopenia	TAF	Tenofovir Alafenamide
HIV	human immunodeficiency virus	TB	tuberculosis
HIVAN	HIV-associated nephropathy	TBA	Total Body Water
HLA-B27	Human Leukocyte Antigen B27	TB-IRIS	TB immune reconstitution inflammatory syndrome

HMGCoA	3-hydroxy-3-methyl-glutaryl-coenzyme A (statin)	TBM	tuberculosis meningitis
HMOD	Hypertension Mediated Organ Damage	TB-NAAT	TB Nucleic Acid Amplification Tests
H2O	water	TBSA	total body surface area
HR	heart rate	TCA	tricyclic antidepressants
HSV	herpes simplex virus	TDD	total daily dose
HT	hormone therapy	TDF	tenofovir disoproxil fumarate
HZO	Herpes Zoster Opthalmicus	TDM	Therapeutic drug monitoring
ICS	inhaled corticosteroid	TEG	Thromboelastography
ICU	intensive care unit	TEN	Toxic Epidermal Necrolysis
IgG	immunoglobulin G	TFT	thyroid function test
IgM	immunoglobulin M	TIA	transient ischaemic attack
IHD	ischaemic heart disease	TIP	transjugular intrahepatic portosystemic
IKRT	Intermittent Kidney replacement therapy	TOP	termination of pregnancy
IM	intramuscular	TP	Treponema pallidum
INR	international normalized ratio	TPHA	Treponema pallidum haemagglutination assay
InSTI	integrase inhibitor	TPN	total parenteral nutrition
IO	Intra-osseous	TPT	tuberculosis preventive therapy
iOS	iPhone Operating System	TSH	thyroid stimulating hormone
IOL	Induction of Labour	TTP-HUS	thrombotic thrombocytopenic purpura-Haemolytic uraemic syndrome
IOP	intraocular pressure	TTR	Therapeutic time in range

IRIS	immune reconstitution inflammatory syndrome	UA	unstable angina
ITP	Immune thrombocytopenia	UDV	unit dose vial
iu	international units	ULN	upper limit of normal
IUCD	intrauterine contraceptive device	UE	ung emulsificans (emulsifying ointment)
IV	intravenous	UPCR	Urine protein to creatine ratio
J	Joule	UTI	urinary tract infection
K	potassium	VAP	ventilator-associated pneumonia
kg	kilogram	VAS	Visual Analogue Scale
kPa	Kilopascal	VBG	Venous Blood Gas
KRT	Kidney Replacement Therapy	VDRL test	venereal disease research laboratory test
KS	Kaposi Sarcoma	VF	ventricular fibrillation
L	litre	VHF	viral haemorrhagic fevers
LABA	long-acting beta2 agonist	VHL	Von Hippel-Lindau
LAM (urine test)	lipoarabinomannan (urine test)	VL	viral load
LBBB	left bundle branch block	VMA	Vanillylmandelic acid
LDH	lactate dehydrogenase	VRS	Verbal rating scale
LDL (-C)	low density lipoprotein (-cholesterol)	VSD	ventricular septal defect
LFT	Liver Function Test	VTE	Venous thromboembolism
LH	luteinising hormone	VT	ventricular tachycardia
LMWH	low molecular weight heparin	VZIG	varicella-zoster immunoglobulin
LP	lumbar puncture	VZV	Varicella zoster virus

LoE	level of evidence	WBOT	Ward-Based Outreach Team
LPV/r	lopinavir/ritonavir	WCC	white cell count
LS	Lifestyle Modification	WHO	World Health Organisation
LV	left ventricular	WHO DAS	WHO Disability Assessment Schedule
		WOCP	women of childbearing potential
		WPW	Wolf-Parkinson-White
		XDR-TB	extensively drug-resistant tuberculosis
		YMRS	Young Mania Rating Scale
		Zn	Zinc

DECLARATION OF INTERESTS

Selection of medicines for the essential medicines list requires measures to ensure that the best possible assessment of scientific evidence is achieved in an independent environment, free of either direct or indirect pressures. Thus, to assure the credibility of the process, it is necessary to avoid situations in which financial or other interests may unduly influence decision-making.

All members of the NEMLC, combined Primary Healthcare/Adult Hospital Level Technical Expert Review Committee and Secretariat were required to make formal declarations of interest on application and at the start of each meeting. Guidance for declaring, assessing and handling conflicts of interests is outlined in the NEMLC conflict of interest policy, accessible at: https://www.health.gov.za/nhi-edp-stgs-eml/.The following specific declarations were noted and managed during the development of the 6th Edition of the Adult Hospital Level STGs and EML:

Combined PHC/Adult Hospital Level Expert Review Committee (2020-2024)	
Dr H Dawood (Vice-Chairperson: 2020-2023)	NICD influenza guidelines: annual. Abbott - TB LAM presentation at SA TB conference 2022
Prof M Blockman	Various pharmaceutical companies provide research sponsorship to the University of Cape Town (nil to member).
Ms SM McGee	Employed by Ophthalmology Society of South Africa (OSSA) which has direct interest in the activities of the PHC/AHL ERC from the point of view of access to and availability of medicines for eye conditions. society receives sponsorships and support from various pharmaceutical and medical device companies.
Dr JS Nel	Public lectures on HIV & COVID topics for Cipla, Abbvie, Novo Nordisk and HIV Clinicians Society. Funding for RECOVERY and InterCOV trials (PI for the trials, but no personal fee taken) - Wellcome Trust, Bill & Melinda Gates Foundation.
Prof L Robertson (Vice- Chairperson from 2023-2024)	Contracted as a technical advisor to the mental health and disability Ghana Somubi Dwumadie Programme funded by UK FCDO. Contracted from 5 June 2024 – 30 September 2024 to conduct phase 4 of work on access to psychotropic medicines in Ghana. Honorarium from Foundation for Professional Development (FPD) to assist FPD and the Knowledge Translation Unit with drafting an application to SAHPRA for rescheduling of fluoxetine.
Prof M Levin	Serves on the executive committee of the Allergy Society of South Africa and is the CEO of the Allergy Foundation of South Africa. He is registered for RWOEE in his role as CEO of AFSA, providing training of doctors for AFSA. He also serves on advisory boards for Sanofi and Takeda and within the last 5 years has also lectured for Organon, Cipla, Abbvie, Glenmark and Pharmadynamics and Bayer. The Allergy Foundation of SA produces and markets low cost spacers for the management of children and adults with asthma.
Dr N Tsabedze	Servier Laboratories SA (Pty) Ltd: Consultancy (New Hypertension Guideline Management); Novartis SA (Pty) Ltd: Consultancy to develop a Heart Failure Tool box; Boehringer–Ingelheim, Novonordisk, Eli-Lilly, AstraZeneca and Adcock Ingram: Speaker Fees for Webinars & Advisory Board Services; Wits University/ NovoNordisk: SELECT Phase III Trial; Wits University/TAKEDA: Research Grant - Fabry's Disease in South Africa; HEFSSA/NPC: Heart Failure Guidelines Committee Member

	(SAMJ).
Dr M Reddy	2022: IQVIA Health – Project regarding Analysis and summary of the reimbursement landscape for HIV – retrospective analysis on ARV reimbursement.

National Essential Medicines List Committee (2020-2024)	
Prof M Blockman	See above
Dr H Dawood	See above
Dr T Kredo	SA- Medical Research Council: Receipt of grants.
Dr M McCaul	International research grants
Prof J Miot	Chair of the Clinical Advisory Board of HQA. HQA is currently investigating outcomes measurement through the setting up of a clinical registry (probably in oncology) which may result in data to inform clinical guidelines in the future.
Mrs B Molongoana	Technical advisor for Market Access Africa/JPIEHGO
Prof L Robertson	See above
Prof P Ruff	Wits University Health Consortium: Clinical trial funding and honoraria from various pharmaceutical companies involved in oncology trials and funds are directed to Wits Health Consortium.
Mr R Wiseman	Employed by Liberty Health

USEFUL NUMBERS AND URL LINKS

POISONS INFORMATION CENTRES	
Poison Information Helpline	0861 555 777 https://www.afritox.co.za/
Red Cross War Memorial Children's Hospital Poisons Information Service	021 658 5308 Email: poisonsinformation@uct.ac.za http://www.paediatrics.uct.ac.za/poisons-information-centre
Tygerberg Poison Information Centre	0861 555 777 www.sun.ac.za/poisoncentre
University of the Free State Poison Control and Medicine Information Centre	082 491 0160
Information on poisons	
COMMUNICABLE DISEASES	
NICD COVID-19 hotline	0800 029 999 http://www.nicd.ac.za/ https://sacoronavirus.co.za/
Rabies hotline (NICD)	0800 212 552
Viral Haemmorhagic Fever outbreak hotline (NICD)	0800 212 552
South African Vaccine Producers National notifiable medical conditions surveillance	011 386 6063/2/00 Helpline/ sms/ whatsapp line: 072 621 3805 Fax: 086 639 1638 Email: NMCSurveillanceReport@nicd.ac.za
MEDICINE INFORMATION CENTRES	
Medicine Information Centre (Cape Town)	021 406 6829 0861 100 531 Email: http://www.mic.uct.ac.za/
Amayeza Info Centre	011 475 2994
National HIV Healthcare Worker Hotline	0800 212 506 021 406 6782
DEPARTMENT OF HEALTH	
National Department Health website	www.health.gov.za
Essential Drugs Programme	https://www.health.gov.za/nhi-hpp-edp/ Email:SAEDP@health.gov.za
Third line ART applications	Email: TLART@health.gov.za
Medicine stock availability reporting	Email: stockalert@health.gov.za
Adverse Drug Reactions: South African Health Products Regulatory Authority (SAHPRA)	adr@sahpra.org.za 012 501 0311 https://primaryreporting.who-umc.org/Reporting/Reporter?OrganizationID=ZA
Central Chronic Medicine Dispensing and Distribution (CCMDD)	https://www.health.gov.za/ccmdd/

USEFUL NUMBERS AND URL LINKS

OTHER NUMBERS

Women abuse helpline	0800 150 150
Child line	116
South African Police Services Crime Stop	10111
National Human Trafficking Helpline	0800 222 777
Suicide helpline	0800 567 567

MISCELLANEOUS

Antiretroviral pregnancy registry	http://www.APRegistry.com/
Antiretroviral therapy: drug-drug interactions	https://www.hiv-druginteractionslite.org/checker http://www.mic.uct.ac.za/
Asthma control test™	https://www.asthmacontroltest.com/
BMI-based CVD risk tool	https://www.framinghamheartstudy.org/fhs-riskfunctions/cardiovascular-disease-10-year-risk/#
COPD: Modified Medical Research Council (mMRC) dyspnea scale calculator	https://www.mdcalc.com/mmrc-modified-medical-research-council-dyspnea-scale `
Dietary phosphate restriction	https://www.kidney.org/
ECG analysis: Reference guide	ECG APPtitude: http://q-r.to/baoxer ECG ONLINE: http://ecgonline.uct.ac.za
eGFR calculator	https://www.kidney.org/professionals/KDOQI/gfr_calculator
Haemophilia centres	http://www.haemophilia.org.za/treatment-centres/
Ideal weight calculator	https://www.mdcalc.com/ideal-body-weight-adjusted-body-weight
Hyponatraemia: Infusion rate calculator	https://reference.medscape.com/calculator/hyponatremia-correction-infusate-rate
Mental health conditions: support groups	www.SADAG.org www.SAFMH.org.za
NSTEMI: Risk stratification calculators	TIMI: http://www.mdcalc.com/timi-risk-score-for-uanstemi/ Grace Risk Score: http://www.mdcalc.com/grace-acs-risk-and-mortality-calculator/
Opioid withdrawal: Objective opioid withdrawal scale (OOWS)	https://familypracticerenewalnl.ca/wp-content/uploads/2023/09/OOWS-Tool-May-2024.pdf
Pain (chronic): Rating scale to measure pain severity, quality of life, and functionality	Pain, Enjoyment and General Activity (PEG) scale: https://health.gov/hcq/trainings/pathways/assets/pdfs/PEG_scale.pdf
Potassium deficit calculator	https://globalrph.com/medcalcs/potassium-deficit-calculator/
QT prolongation: Medicines causing QT prolongation	https://www.sads.org.uk/drugs-to-avoid/?doing_wp_cron=1585301751.3996679782867431640625
Renal impairment: Medicines requiring dose adjustment in renal impairment	http://www.globalrph.com/index_renal.htm
Substance use disorder: rating scales	ASSIST: https://www.who.int/publications/i/item/9789241594938-2 DUDIT: https://www.emcdda.europa.eu/system/files/attachments/12173/DUDIT-English-version.pdf

Valproate: acknowledgement of risk form	https://www.sahpra.org.za/wp-content/uploads/2025/05/GLF-CEM-PV-S01_v2-Valproate-Annual-Risk-Acknowledgement-Form-ARF.pdf
Vertigo: benign paroxysmal positional vertigo diagnosis	Dix-Hallpike test: https://www.youtube.com/watch?v=8RYB2QlO1N4 Epley manoeuvre: https://www.youtube.com/watch?v=jBzID5nVQjk
VTE: Risk assessment tools	Padua Prediction Score: https://www.mdcalc.com/padua-prediction-score-risk-vte IMPROVE VTE risk score: https://www.outcomes-umassmed.org/IMPROVE/risk_score/vte/index.html Geneva risk score: https://www.mdcalc.com/geneva-risk-score-venous-thromboembolism-vte-prophylaxis
Water deficit calculator	https://www.msdmanuals.com/professional/multimedia/clinical-calculator/water-deficit-in-hypernatremia