The Bleeding Patient

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The Bleeding Patient

If you prick us, do we not bleed?

The Bleeding Patient

Disorders of primary homeostasis:

dysfunction of the processes involved in formation of the platelet plug due to abnormalities of:

- platelet number
- platelet adhesion
- platelet aggregation

Disorders of secondary homeostasis:

dysfunction of the processes involved in humoral coagulation due to abnormalities of:

- coagulation factors
- contact factors
- fibrinogen
- connective tissues

The Bleeding Patient

Disorders of Primary Homeostasis

Hereditary :

- von Willebrands disease
- Wiskott-Aldrich syndrome

Iatrogenic:

- post-transfusion
- drug-induced immune thrombocytopaenia
- drug-induced qualitative platelet dysfunction

Acquired:

- ITP
- DIC
- aplastic anaemia
- hypersplenism
- uraemia
- mechanical (cardiac bypass; AS)

The Bleeding Patient

Disorders of Secondary Homeostasis

Coagulation factor abnormalities :

- Haemophila A and B
- deficiencies of factor II, V, VII, X, XIII
- acquired inhibitors to coagulation factors

Fibrinogen Abnormalities:

- afibrinoginaemia/hypofibrinogenaemia/dysfibrinogenaemia
- hyperfibrinolysis

CT disorders:

- Ehlers-Danlos syndrome
- Osler-Weber-Rendu syndrome
- scurvy

The Bleeding Patient

Disorders of Homeostasis

- bone marrow dysfunction
- drug-related

- ITP

- TTP

EBOLA!

Bone marrow

- Myelodysplasia
  - 2005 Indian study found myelodysplasia in 32% on BMAT
  - Ugandan autopsy study found megakaryocyte myelodysplasia in 84%
  - 2013 Indian study did not show megakaryocyte dysplasia

Dhurve SA and Dhurve AS. Mediterr J Hematol Infect Dis 2013; 5

Nabadda, S. East African Medical Journal 2011; 88 (1)

Bone marrow

- Infiltration
  - may be the result of infection
    - TB; MAC; fungi causing granulomatous inflammation
  - or malignancy
    - lymphoma
  - BMAT is a useful investigation
    - diagnositc yield = 47%
    - unique diagnosis = 33%

Van Schalkwyk WA, Opie J, Novitzky N. Int J Lab Hem 2011; 33

Drugs

- Co-trimoxazole
- INH
- Rifampicin
- Amphotericin B
- Fluconazole
- Warfarin
- Penicillin
- Tricyclic antidepressants
- Too much garlic, vitamin E, vitamin C or ginger

Thrombocytopaenia

- Thombocytopaenia is common in HIV infection
  - Pre-HAART era:
    - incidence of 5-30%
    - initial manifestation of HIV in 10%
    - association between HIV and ITP predates identification of the virus
  - Heparin and drugs used for OI's may cause thrombocytopaenia

Liebman, H. Hematology 2008

Immune Thrombocytopaenia

- Platelet count <150 x 10^9/l
- More prevalent in :
  - advanced HIV infection (CD_4 < 200/µl)
    - CD_4 > 700: 2.8%
    - CD_4 <200: 10.8%
  - clinical AIDS
  - injection drug users
  - Age > 45
  - lymphoma and/or anaemia

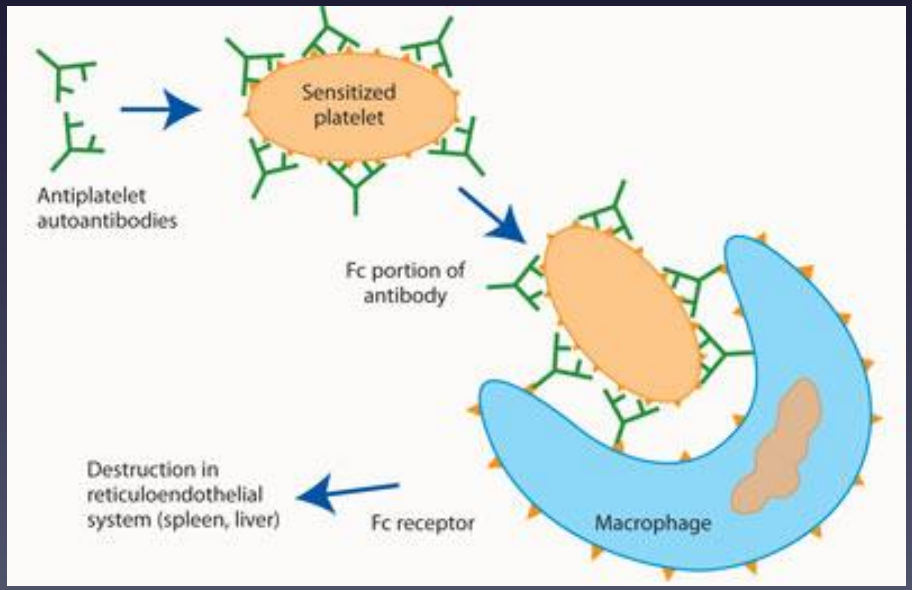
Kaslow RA. A report from the Multicenter AIDS Cohort Study. Ann Intern Med. 1987;107

Sloand EM. Eur J Haematol. 1992;48

Sullivan PS. J Acquir Immune Defic Syndr Hum Retrovirol. 1997;14

Immune Thrombocytopaenia

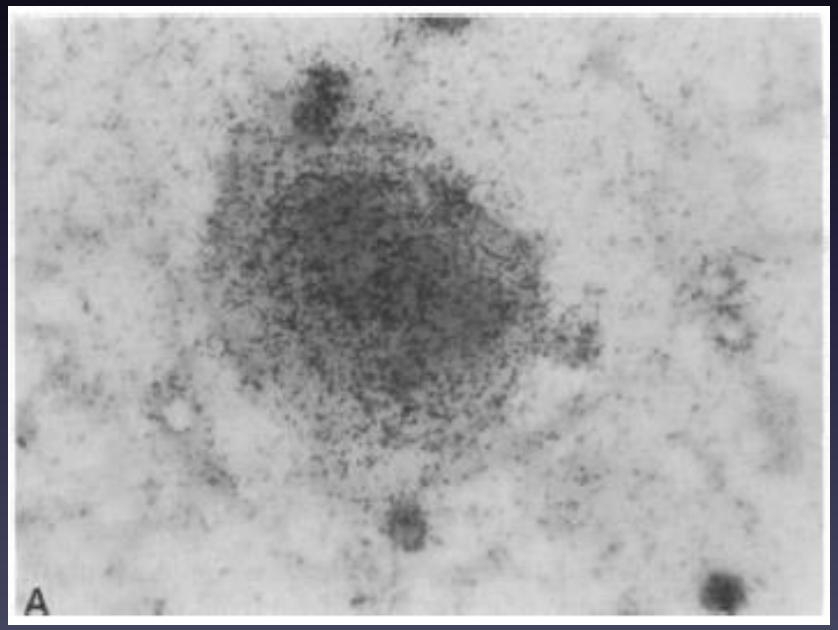
- Immune complex formation
- Cross reacting anti-HIV antibodies
- Anti-GPIIIa antibodies

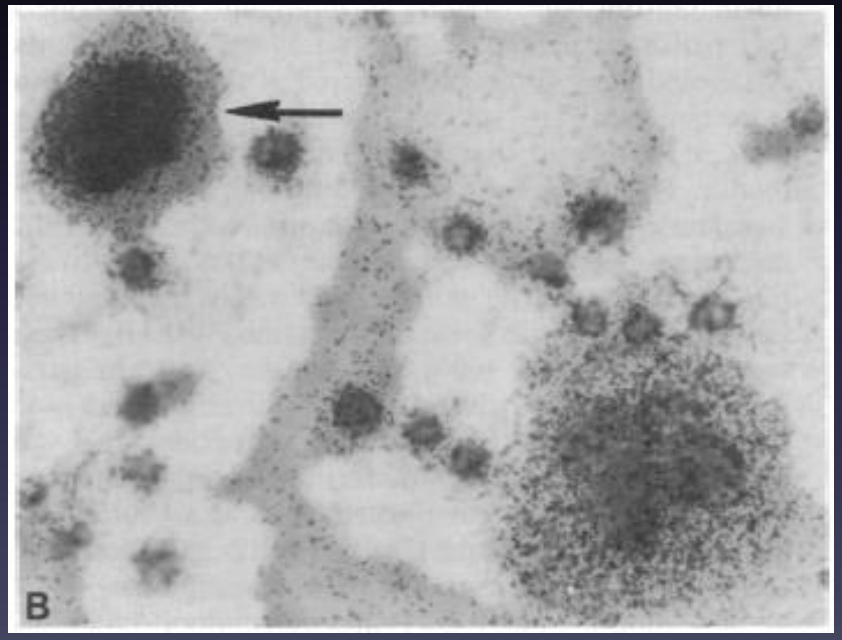


Cines DB, Semin Hematol. 2009 January ; 46(1 Suppl 2)

Immune Thrombocytopaenia

- Decreased platelet production and ineffective haematopoesis





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Li Z. Blood. 2005; 106

Immune Thrombocytopaenia

- Bleeding
  - mucosal; skin; intracranial
  - uncommon with platelets >30 x 10^9/l
- Features of other secondary causes of ITP
  - SLE; Hep C, lymphoma
- Drug history

Immune Thrombocytopaenia

- Peripheral blood:
  - low platelets (normal or large); normal WCC and Hb
  - exclude fragments; clumping and satellitism
- Bone marrow:
  - normal or increased numbers of megakaryocytes, increased immature forms
  - megakaryocyte apoptosis
- Reticulocyte count and Coombs to exclude associated AIHA

Immune Thrombocytopaenia

- Corticosteroids
- IVIg
- Anti-Rh(D)
- HAART
- Rituximab
- Thrombopoetin receptor agonists
- Splenectomy

Kistanguri, G and McCraeKR, Hematol Oncol Clin North Am . 2013 June ; 27(3)

Immune Thrombocytopaenia

- Corticosteroids
  - 80% respond
  - most relapse
  - higher doses = more sustained response

Kistanguri, G and McCrae KR, Hematol Oncol Clin North Am . 2013 June ; 27(3)

Immune Thrombocytopaenia

- IVIg
  - used in conjunction with corticosteroids
  - rapid increase in platelet count
  - response of short duration
  - toxicity: aseptic meningitis, nephrotoxicity, thrombosis, haemolytic anaemia

Kistanguri, G and McCraeKR, Hematol Oncol Clin North Am . 2013 June ; 27(3)

Immune Thrombocytopaenia

- Anti-Rh(D)
  - binds erythrocytes leading to clearance in the spleen
  - inhibits clearance of opsonised platelets
  - only effective in patients who are Rh(D) positive with intact spleens
  - complicated by haemolysis and fall in Hb

Kistanguri, G and McCraeKR, Hematol Oncol Clin North Am . 2013 June ; 27(3)

Immune Thrombocytopaenia

- HAART
  - HIV-related cytopaenis correlate with plasma viral load
  - AZT monotherapy increases platelet counts in 60-70%
  - HAART induces sustained platelet responses

Liebman, H. Hematology 2008

Immune Thrombocytopaenia

- Rituximab
  - anti- CD20 monoclonal antibody
  - median response time 5.5 weeks; median duration 10.5 months
  - durable response in 21% of patients
  - adverse effects include infusion reactions, serum sickness and cardiac arrhythmias
  - contraindicated in chronic Hep B infection

Kistanguri, G and McCraeKR, Hematol Oncol Clin North Am . 2013 June ; 27(3)

Immune Thrombocytopaenia

- Thrombopoetin receptor agonists
  - for refractory patients? for newly diagnosed patients? before or after splenectomy
  - Romiplostim; Eltrombopag
  - stimulate megakaryocyte proliferation and differentiation

Kistanguri, G and McCraeKR, Hematol Oncol Clin North Am . 2013 June ; 27(3)

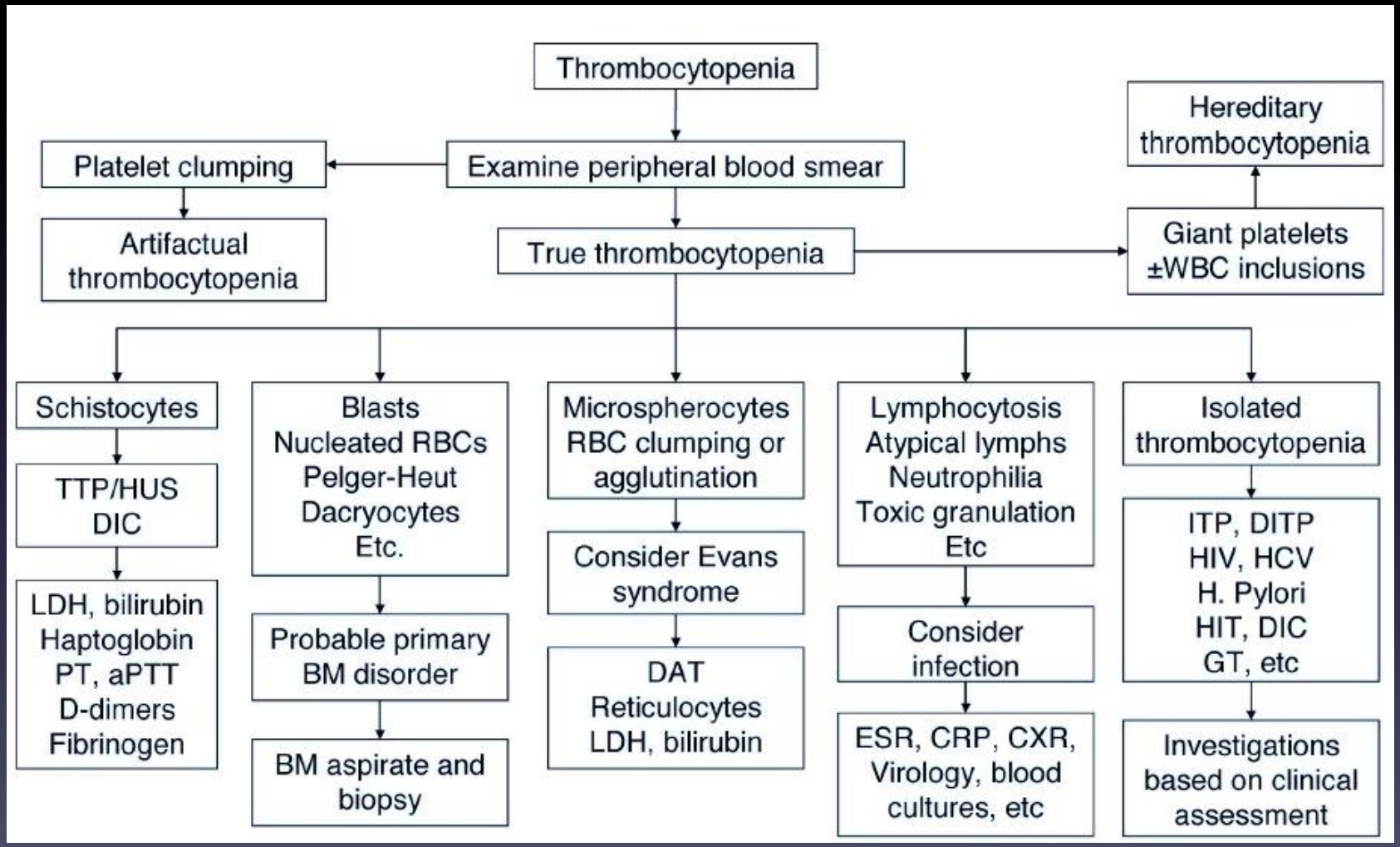
Immune Thrombocytopaenia

- Splenectomy
  - safe and effective in HIV+ patients
  - complete response 66% - 72%
  - most relapses in first 2 years

Kistanguri, G and McCraeKR, Hematol Oncol Clin North Am . 2013 June ; 27(3)

Liebman, H. Hematology 2008

Investigation of Thrombocytopaenia

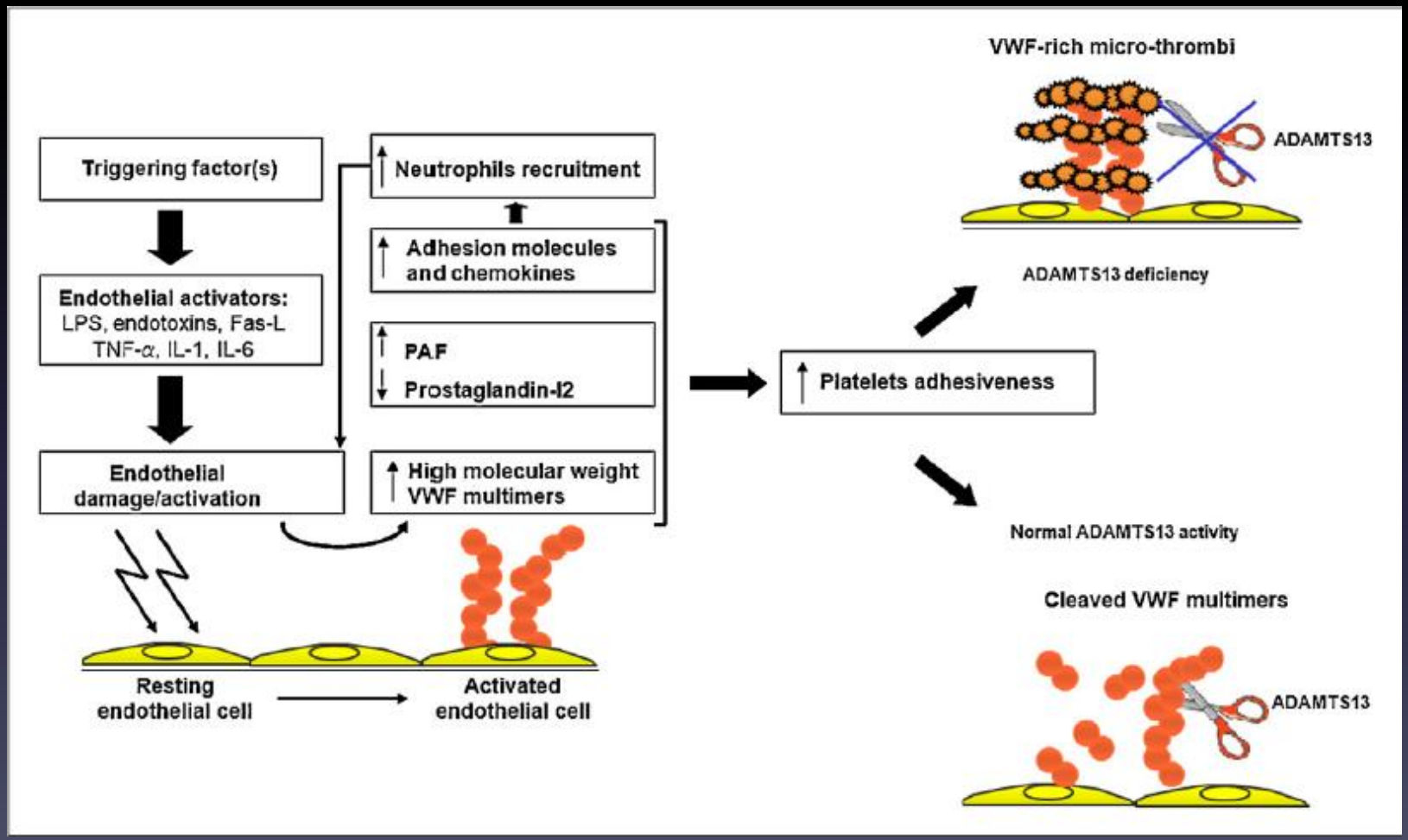


Roberto Stasi. Hematology 2012

Thrombotic Thrombocytopaenic purpura

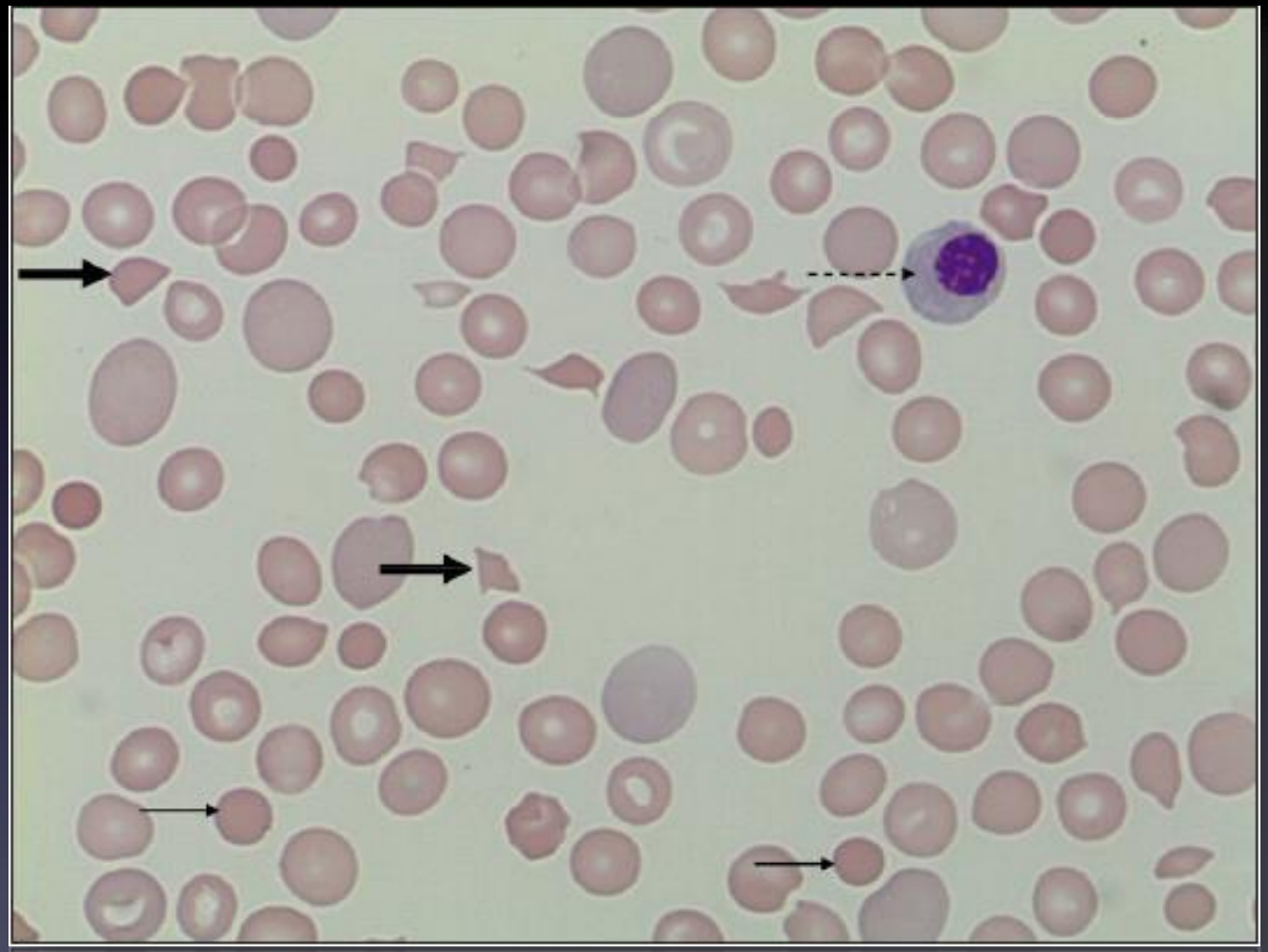
- Thrombotic microangiopathy caused by a deficiency of ADAMTS 13 (activity <10%)
  - A Disintegrin And Metallopoteinase with Thrombospondin-1 motifs, member 13
  - von Willebrands factor cleaving protease
  - auto-antibodies to ADAMTS 13
  - highly adhesive ultra-large vWF multimers

Thrombotic Thrombocytopaenic purpura



Coppo, P and Veyradier, A. Presse Med. 2012; 41: e163–e176

Thrombotic Thrombocytopaenic purpura



Opie, J. SAMJ June 2012, Vol. 102, No. 6

Thrombotic Thrombocytopaenic purpura

- Incidence of 4/ 1 000 000 per year
- association with HIV, CT disorders, cancer, pregnancy, treatment with antiplatelet drugs
- young black women with high viral loads
- HIV+ patients with few or no AIDS related complications do better

Coppo, P and Veyradier, A. Presse Med. 2012; 41: e163–e176

Opie, J. SAMJ June 2012, Vol. 102, No. 6

Thrombotic Thrombocytopaenic purpura

Classic Pentad

thrombocytopaenia

microangipathic haemolytic anaemia

fever

fluctuating neurological signs

renal dysfunction

Coppo, P and Veyradier, A. Presse Med. 2012; 41: e163–e176

Blombery, P and Scully, M. Journal of Blood Medicine 2014: 5 15-23

Thrombotic Thrombocytopaenic purpura

- Plasma exchange
  - achieves remission rates of 85%
  - efficacy due to replenishing ADAMTS13
  - superior to plasma infusion
    - response @ D9: 47% vs 27%
    - survival @ 6/12: 78% vs 47%
  - should be initiated without delay

Coppo, P and Veyradier, A. Presse Med. 2012; 41: e163–e176

Blombery, P and Scully, M. Journal of Blood Medicine 2014: 5 15-23

Thrombotic Thrombocytopaenic purpura

- HAART
- Corticosteroids
  - sound theoretical basis
  - response to high dose methylprednisolone better than low dose
  - some clinical trials show similar outcomes regardless of steroid use

Coppo, P and Veyradier, A. Presse Med. 2012; 41: e163–e176

Blombery, P and Scully, M. Journal of Blood Medicine 2014: 5 15-23

Thrombotic Thrombocytopaenic purpura

- Antiplatelet agents
  - some studies show a trend towards better survival with aspirin and dipyridamole
  - others report no effect and an increased risk of bleeding

Coppo, P and Veyradier, A. Presse Med. 2012; 41: e163–e176

Blombery, P and Scully, M. Journal of Blood Medicine 2014: 5 15-23

Refractory TTP

- Refractory TTP can be defined as no response after 4 full days of therapy
- An exacerbation can be defined as worsening of disease
    - on treatment
    - while decreasing the plasmapheresis schedule
    - if the platelet count has been >30 for less than 30 days
- Relapse is worsening of the condition when the platelet count has been >30 for more than 30 days

Coppo, P and Veyradier, A. Presse Med. 2012; 41: e163–e176

Therapy for Refractory TTP

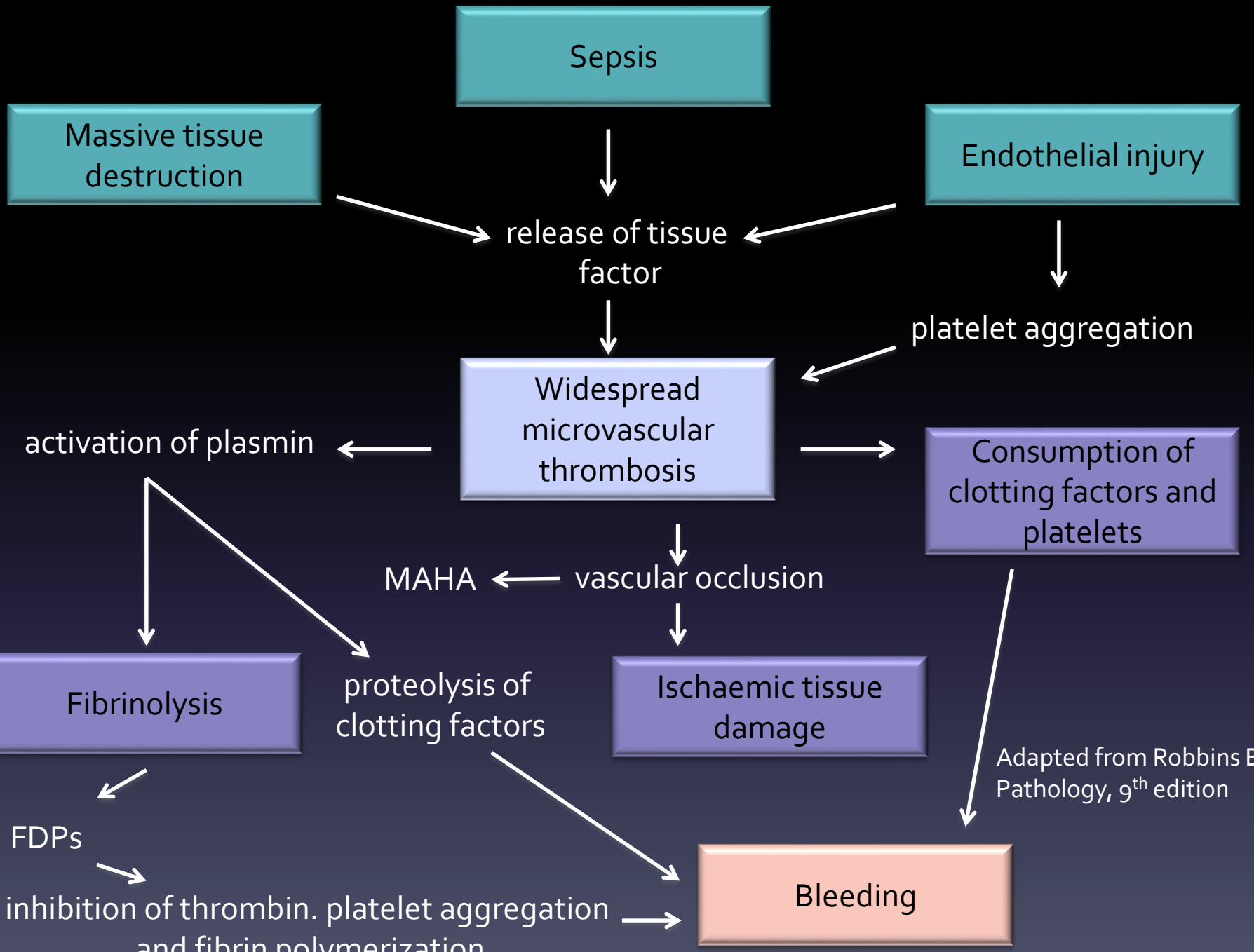
- Rituximab
  - refractory:
    - complete remission achieved in 88%
    - recovery of ADAMTS13 activity and decrease in antibody production
  - relapse:
    - complete remission in 100%

Coppo, P and Veyradier, A. Presse Med. 2012; 41: e163–e176

Blombery, P and Scully, M. Journal of Blood Medicine 2014: 5 15-23

Disseminated Intravascular Coagulation

- systemic activation of coagulation with formation of thrombi in the microcirculation
- platelets and coagulation factors are consumed
- fibrinolysis is activated
- usually triggered by
  - i) release of tissue factor or thromboplastic substance or
  - ii) widespread endothelial damage


Sepsis
Massive tissue destruction
Endothelial injury
release of tissue factor
platelet aggregation
Widespread microvascular thrombosis
activation of plasmin
Consumption of clotting factors and platelets
MAHA
vascular occlusion
Fibrinolysis
proteolysis of clotting factors
Ischaemic tissue damage
FDPs
inhibition of thrombin. platelet aggregation and fibrin polymerization
Bleeding
Adapted from Robbins Basic Pathology, 9th edition

Therapy for DIC

- Treatment of the underlying condition
- Supportive care
  - platelet transfusion
  - FFP infusion
  - cryoprecipitate infusion
  - anticoagulation

Wada H et al. J Thromb Haemost 2013; 11: 761–7.