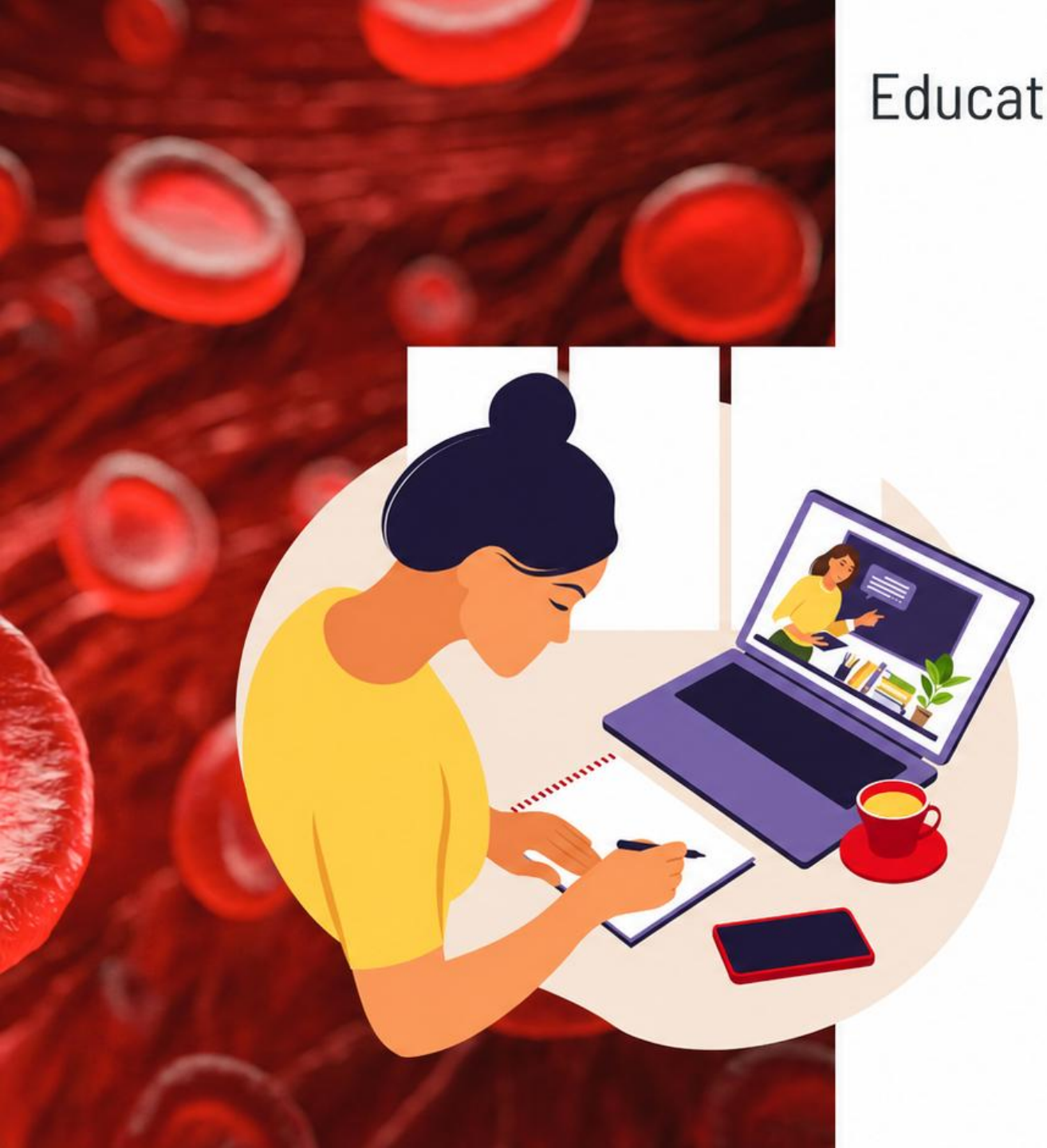


Educational Courses

BHS

Acquired bleeding disorders

Cédric Hermans (UCLouvain)

ACQUIRED BLEEDING DISEASES

Cedric HERMANS

MD, PhD, FRCP (Lon, Edin)
Brussels, BELGIUM

UCLouvain

INSTITUT DES MALADIES RARES
Cliniques universitaires SAINT-LUC I UCL Bruxelles

Cliniques universitaires SAINT-LUC UCL BRUXELLES

Causes of bleeding tendency

Thrombocytopenia

Thrombopathy

Clotting factor(s) defect (s)

Increased fibrinolysis

Collagen / vascular disease

Unknown cause



BLEEDING DISORDERS

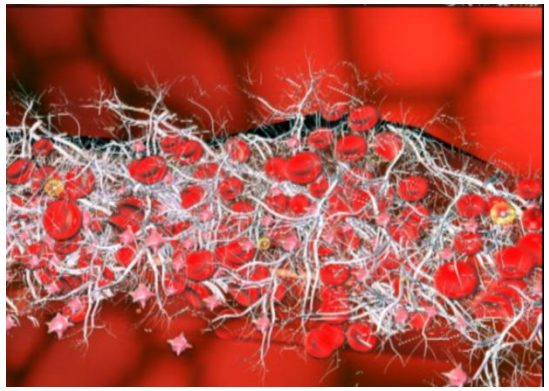
- **Acquired (frequent)**
  - Overanticoagulation
  - Liver failure
  - Disseminated intravascular coagulation (DIC)

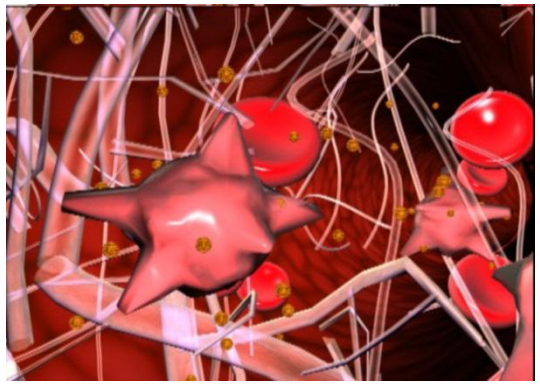
- **Acquired (rare)**
  - Acquired Haemophilia
  - Acquired VWD
  - Acquired FX deficiency

- **Inherited (rare or very rare)**
  - Haemophilia A and B
  - Von Willebrand disease
  - FVII, FXI, FII, … deficiency (rare)
  - FXIII deficiency



Thrombus formation

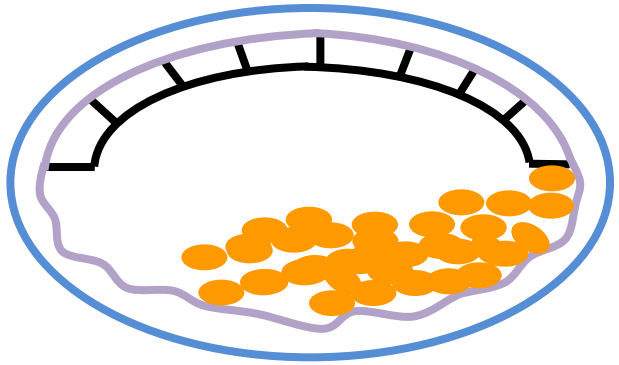


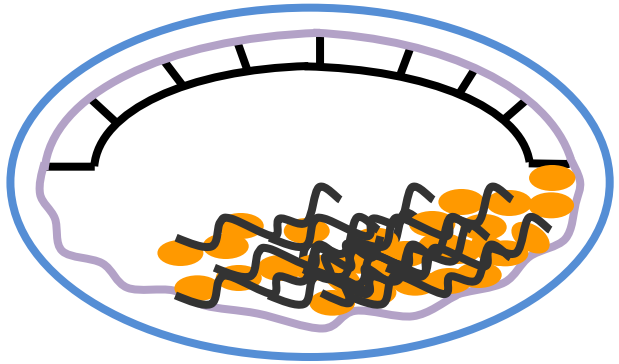


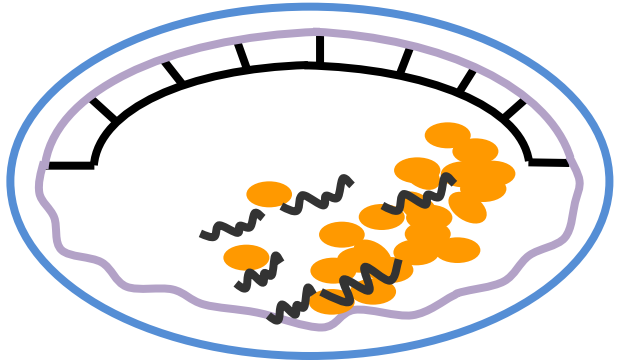
1. Platelet plug
Primary haemostasis

2. Fibrin Formation
Coagulation cascade

3. Destruction
Fibrinolysis

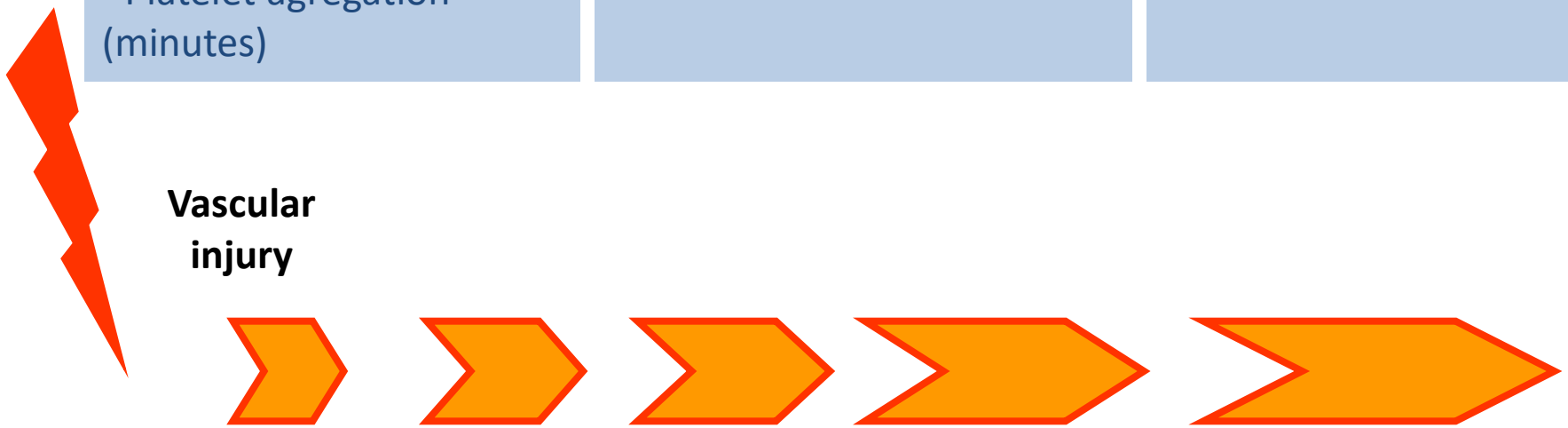






Physiology of haemostasis

Primary Haemostasis	Secondary Haemostasis	Fibrinolysis
- Vasoconstriction (immediate) - Platelet adhesion (seconds) - Platelet agregation (minutes)	- Activation of coagulation factors - Fibrin formation (minutes)	- Activation of fibrinolysis (minutes) - Clot lysis (hours)



Mechanisms of acquired bleeding diseases

Primary Haemostasis (platelets and VWF)

- **Decreased production or consumption** (Thrombocytopenia)

- **Functional defect** (Thrombopathy)

- **Acquired VWF deficiency**

Secondary Haemostasis (clotting factor(s))

- **Defect of multiple clotting factors**
  - increased consumption (DIC)
  - decreased production (Liver)
  - inhibition (heparins)
  - altered production (VKAs)

- **Direct inhibition** (Direct oral anticoagulants)

- **Immune reaction to a clotting factor** / auto-antibodies against FVIII – FXIII

- **Absorption of a clotting factor** (FX)

Fibrinolysis

- **Activation/increased of fibrinolysis**



Female 74-year-old with amyloidosis

- **Admitted with cardiac failure and peri-orbital hematomas**

- Hb : 14.6 g/dl
- WCC : 16450/µL
- Platelet count : 341.000/µL

- Elevated troponin and BNP

- Monoclonal band

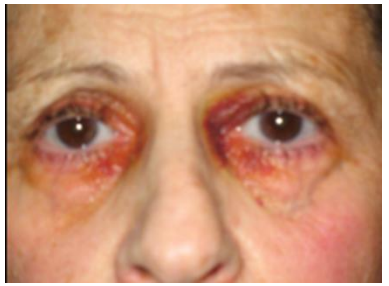
- BM : 6 % abnormal plasmocytes

- Cardiac MRI : typical amyloid cardiomyopathy

- APTT, PT and TT : normal

- FX : 75 %
- FVIIIc : > 200 %
- FXI : 172 %

- **ELT (euglobulin lysis time) : 60 min (normal > 180)**



Systemic hyperfibrinolysis associated with amyloidosis

Male 62-year-old with bleeding after prostate biopsy

- **Bruising since 4 years**
- **Post-traumatic extensive haematoma left leg 2 years ago**

- Hb : 9.5 g/dL
- **APTT : 38 sec**
- **FVIIIc : 40 % (50-150 sec)**

- **Von Willebrand factor : 70 % (Antigen) and 5 % (Activity)**

- Monoclonal IgM Kappa

- Bone marrow biopsy : CLL

Acquired von willebrand disease
Underlying CLL

Male 66-year-old with MM

- **Bruising – conjonctival haemorrhage**

- Proteinuria 2500 mg/24h
- Bleeding after kidney biopsy

- Amyloidosis

- APTT : 35 sec
- **INR : 1.4**
- **Factor X : 46% (normal value > 70 %)**



Acquired FX deficiency - amyloidosis

Bleeding in myeloid disorders

- **Platelet functional defects**
  - *Myelodysplasia*
  - *Polycythemia Rubra Vera (PRV)*
  - *Essential Thrombocytosis (ET)*
- **Thrombocytopaenia**
- **Consumptive coagulopathy**
  - *Acute leukaemia*



Acute myeloid leukemia

Thrombocytopenia and platelet dysfunction

- **Thrombocytopenia** is the most frequent cause of bleeding in patients with AML

- Threshold for platelet transfusion in patients with AML
  - 10-20.000 /µL in absence of bleeding
  - 50.000/µL in case of bleeding

- **Intrinsic platelet functional defects** (thrombopathy) are frequent in patients with AML and contribute to bleeding

- Chemotherapy, antibiotics, circulating fibrin degradation products (FDPs) can contribute to platelet dysfunction and failure of platelet plug formation



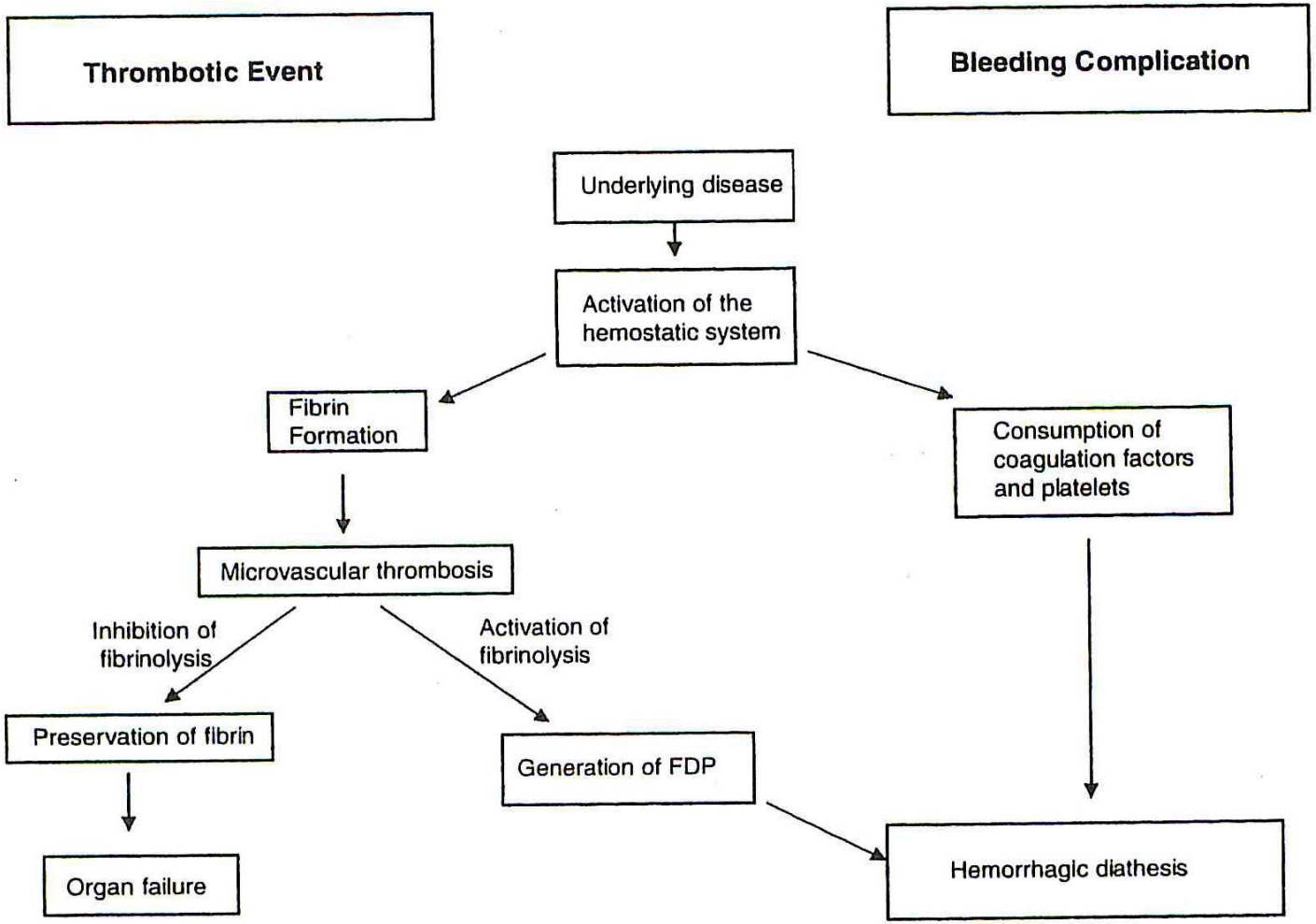
Acute myeloid leukaemia

Disseminated intravsacular coagulation (DIC)
Defibrination syndrome

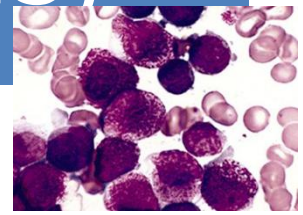
- **DIC frequent in patients with AML (15%)**
- Much more frequent in patients with Acute Promyelocytic Leukaemia (APL – AML M3)
- **Mechanisms by which APL cells induce DIC**
  - Induction of fibrinolysis (cleavage of plasminogen into plasmin)
  - Release of Tissue Factor (TF)
  - Production of cytokines (IL-1)
  - Release of proteases (Elastase)

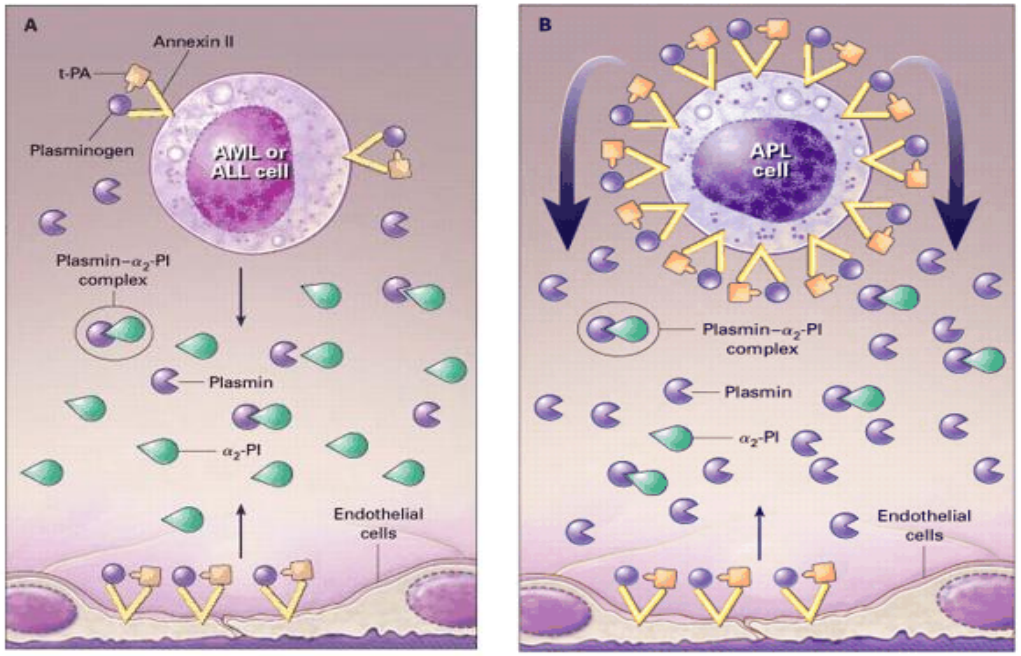


Sequence of events occurring in DIC



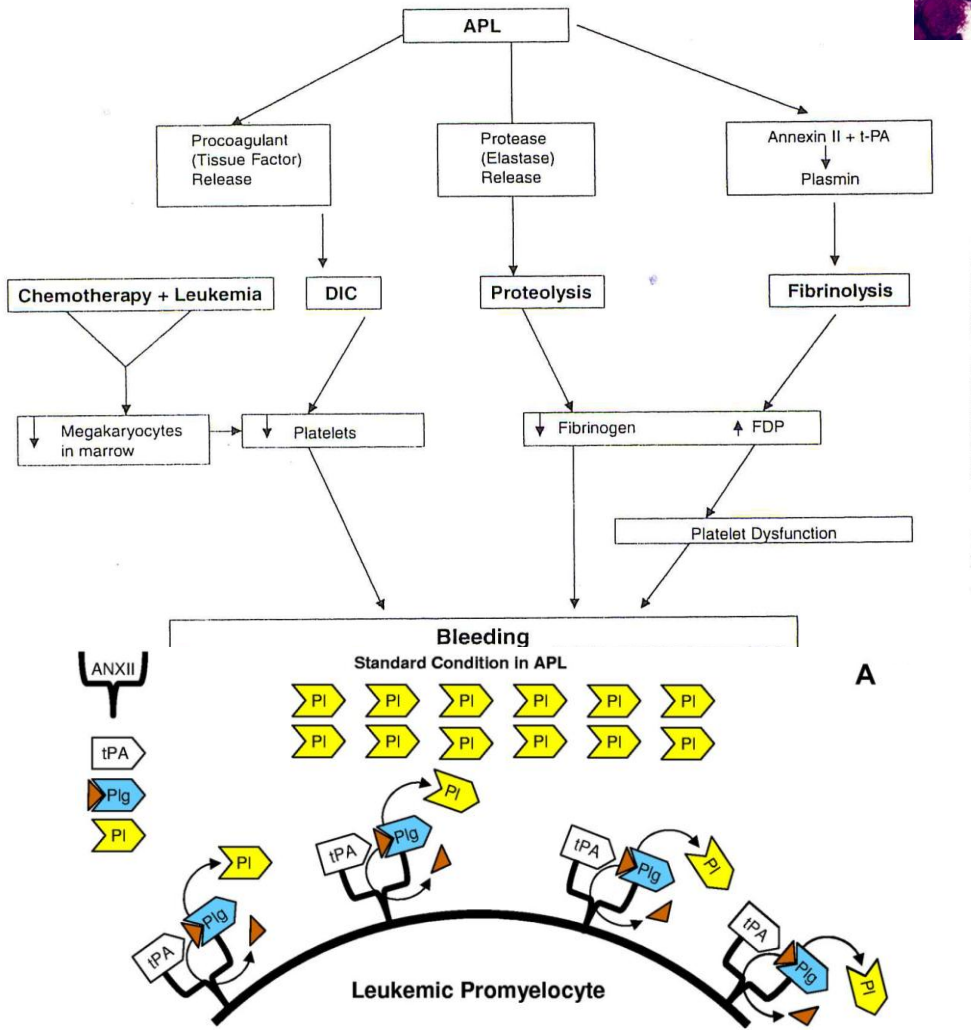
Coagulopathy in patients in APL (AML-M3)





Hyperfibrinolysis in APL (AML-M3)

Mennell J, et al. *NEJM* 1999;340:994-1004



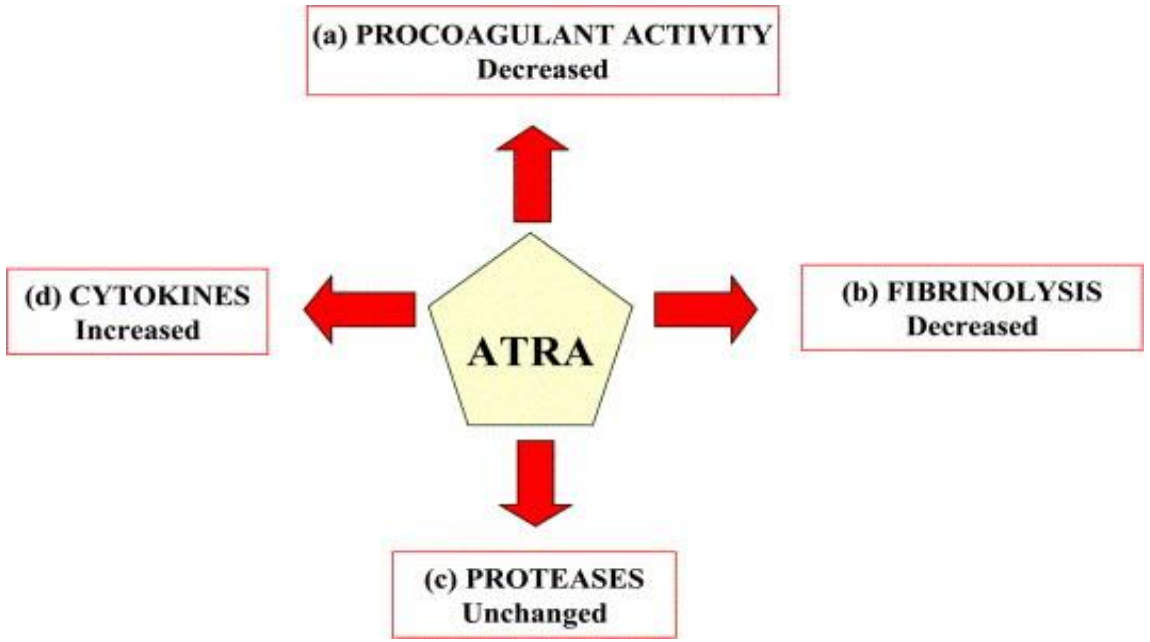
Comment on Jácomo et al, page 207

Coagulopathy in APL: a step forward?

Giuseppe Avvisati UNIVERSITY CAMPUS BIO-MEDICO

All-trans-retinoic-acid (ATRA) and APL

- ATRA promotes terminal differentiation of leukemic promyeloyctic cells
- ATRA has raised the complete remission rate of patients with APL to > 90 % along with prompt improvement of the coagulopathy
- ATRA decreases the cellular expression of procoagulant factors such as TF
- Cytokine production is increased after ATRA treatment (implicated in thrombotic complications)



Arbuthnot C & Wilde JT. *Blood Rev* 2006;20:289-297

Baseline laboratory tests in patients with Acute Leukaemia



Tests	Use(s) and significance
PT, APTT, Fibrinogen	Severity of coagulopathy
Platelet count	Bleeding time not necessary
D-Dimer (Euglobulin Lysis Time)	Secondary fibrinolysis
(Alpha2-antiplasmin)	Secondary fibrinolysis

Laboratory tests in patients with Acute Leukaemia

Severity of DIC	Abnormal tests
Mild DIC	Fibrinogen (abnrormally) normal APTT shortened Minimally elevated D-dimers
Florid DIC	PT and APPT prolonged Reduced Fibrinogen AT and protein C reduced Low platelet count
Systemic fibrinolysis	Very low level of fibrinogen



Management of DIC and defibrination syndrome



No active bleeding	Active bleeding
Fresh Frozen Plasma Fibrinogen concentrate Fg level > 100 mg/dl	 Fg level > 125 mg/dl
Platelet concentrates Platelet count > 20.000/µL	 Platelet count > 50.000/µL
Fresh Frozen Plasma APTT < 1.5 times control	 Normal APTT

Management of DIC and defibrination syndrome

Other treatments	Indications
Heparin (Low Dose)	Rapid destruction of Fg and platelets Thrombotic complications
Antifibrinolytic agents (Tranexamic acid – Exacyl)	Very short ELT (< 30 min)

Chronic myeloproliferative disorders

Polycythemia Rubra Vera, Myelofibrosis, CML and ET

- Patients with MPD have an increased risk of bleeding due to **platelet dysfunction**
- Excessive bleeding is reported in 15 % of patients with MPD, most often in patients with ET
- **Acquired VWF deficiency should be excluded**
- Bleeding is uncommon in patients with CML during the chronic phase
- Management of bleeding in patients with MPD and thrombocytosis involves normalisation of the platelet count
- Fibrinolytic agents should be used with caution in patients with MPD (? Potentiation of the risk of thrombosis).



Lymphoproliferative disorders

- Patients with lymphoproliferative disorders are more troubled with **excessive bleeding that arterial or venous thrombosis**

- Causes of bleeding are multiple :

  - Thrombocytopenia (bone marrow disease / chemotherapy)

  - Acquired platelet, coagulation and fibrinolytic abnormalities have been described



Acute lymphocytic leukaemia

DIC

- **DIC is frequent in all type of acute lymphocytic leukaemia (ALL)**
- Affects 5-10 % of children and adults
- More frequent in patients with T-cell leukaemia
- Higher incidence after initiation of chemotherapy



Acute lymphocytic leukaemia

Asparaginase-induced coagulopathy

- **L-asparaginase inhibits protein synthesis (coagulation factors and their inhibitors)**

- Clinical manifestations :

  - Bleeding may occur a few days after completion of treatment (prolongation of PT, APTT and reduction of Fg)
  - Thrombosis occurs later (2-3 weeks) and has been linked to decreased levels of AT
  - Both bleeding and thrombo-embolic events show a predilection for the central nervous system (CNS) : intra-cerebral haemorrhage and cerebral venous thrombosis

- **Therapy of L-asparaginase-induced coagulopathy remains controversial**
  - FFP
  - Antithrombin concentrate
  - Noy yet known whether this treatment reduces thrombosis of the cerebral veins

CLL/ Lymphoma
ITP

- Incidence
  - 10 % of patients with CLL
  - 2 % of patients with Hodgkin disease
  - Occasionnally reported in patients with NHL

- Often associated with activity, may predate diagnosis or appear long after complete remission

- Caused by immune dysregulation in chronic lymphoproliferative diseases

- Standard therapy
  - Corticosteroids
  - Splenectomy
  - IS agents

  - Agressive treatment of the underlying lymphoproliferative does not always correct the ITP
  - A search for recurrent lymphoma is warranted when ITP develops in patients previously treated for HD

Chronic lymphocytic leukemia / lymphoma

Acquired von willebrand disease

- **Acquired VWD is much less common than hereditary VWD**

- Blood tests
  - Prolonged bleeding time and PFA-100 (ADP)
  - Reduction of FVIIIc, VWF antigen and activity

- AVWD has been reported in patients with :
  - CLL / B-cell lymphoma / Plasma cell myeloma

- Mechanisms
  - Anti-VWF antibodies (often IgG) that react with the high-molecular-weight multimers
  - Adsorption of plasma VWF on the surface of neoplastic lymphoid cells

- Treatment
  - DDAVP
  - VWF concentrates
  - High dose immunoglobulins
  - Plasma exchanges
  - Splenectomy



Acquired von Willebrand’s disease

- **Malignant diseases**
  - Monoclonal gammopathy of unknown significance
  - Multiple Myeloma
  - Non-Hodgkin's lymphoma
  - Chronic lymphocytic leukemia
  - Waldenstrom's macroglobulinemia
  - Essential thrombocythemia
  - Polycythemia vera
  - Chronic myelogenous leukemia
  - Wilms tumor
  - Other carcinomaS
- **Immunologic disorders**
  - Systemic lupus erythematosus
  - Other autoimmune diseases
- **Other disorders**
  - Hypothyroidism
  - Ventricular septal defect
  - Aortic stenosis
  - Mitral valve prolapse
  - Gastrointestinal angiodyplasia
  - Uremia
  - Hemoglobinopathies
- **Drugs and other agents**
  - Valproic acid
  - Antibiotics



Multiple myeloma and Waldenström macroglobulinemia

- Abnormal blood tests are frequent in patients with MM and Waldenstöm Macroglobulinemia
- Severe bleeding is uncommon
- Bleeding more likely if :
  - IgA paraproteins
  - Kappa (rather than gamma) light chains
  - High levels of serum proteins
  - Markedly increased serum viscosity
- Therapy
  - Treatment of the underlying disorder in order to reduce or eliminate pathologic immunoglobulins and reduce plasma viscosity
  - Intensive plasma-exchanges may be necessary to control bleeding



Hemostatic defects associated with Monoclonal proteins

Effect on hemostasis	Assay
Inhibition of platelet aggregation	PFA; Bleeding time (prolonged)
Inhibition of fibrin polymerization	Thrombin time (prolonged)
Acquired von Willebrand disease	VWF activity and antigen (lower levels)
Acquired factor X deficiency	Factor X activity (low level)



Multiple myeloma and Waldenström macroglobulinemia

Monoclonal proteins with anticoagulant activity

- **Thrombin inhibitor**
  - High-titer IgG inhibitor with a specific anti-thrombin effect
  - Prolonged thrombin time and reptilase time
  - Plasmapheresis useful to improve coagulation

- **Circulating heparin-like anticoagulant**
  - Associated with severe bleeding
  - Prolongation of thrombin time but not of reptilase time
  - Treatment : chemotherapy, intensive plasma exchanges, intravenous protamine sulfate



Amyloidosis

- **10 % of patients with systemic amyloidosis have severe bleeding (easy bruisability)**
- Bleeding may result from amyloid infiltration of blood vessels
- Abnormalities of laboratory tests are frequent in patients with amyloidosis but not predictive of bleeding



Amyloidosis and acquired bleeding disorders

- **Factor X deficiency**
  - FX as low as 2-4 % (absorption on amyloid fibrils) has been reported
  - Treatment : splenectomy, chemotherapy
- **Chronic systemic fibrinolysis**
  - Absorption of alpha2 –antiplasmin on amyloid fibrils,
  - Elevated levels of t-PA, decrease PAI-1 (Vascular damage ?)
  - Treatment : antifibrinolytic agents
- **Anti-FVIII antibody**
- **Interference of Bence Jone protein with fibrin polymerization**



- **RISK of bleeding during liver biopsy should be considered**

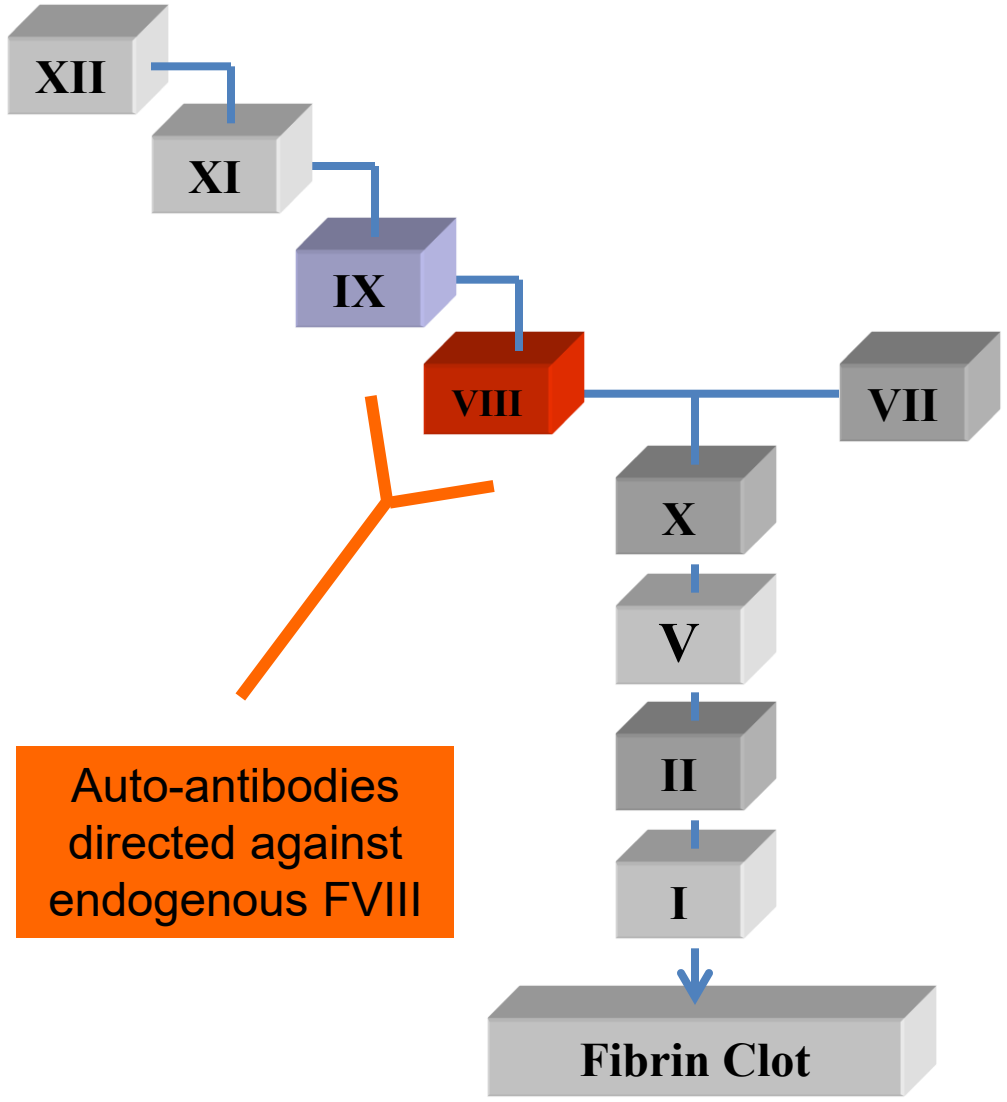
Amyloidosis : Bleeding laboratory work-up

- APTT, PT, TT
- ELT (Euglobulin Lysis Time)
- Alpha-2 antiplasmin
- **In a patient with primary hyperfibrinolysis and normal liver function, amyloidosis should be considered**



ACQUIRED HAEMOPHLIA A : A FREQUENTLY UNDER-DIAGNOSED AUTO-IMMUNE DISEASE

Test	Results
APTT	**Prolonged +++**
Prothrombin time	Nl
Thrombin time	Nl
Fibrinogen	Nl
D-dimers	Increased
Platelets	Nl



AHA is an autoimmune disease caused by the spontaneous production of neutralising immunoglobulin G (IgG) autoantibodies (inhibitors) targeting endogenous FVIII.

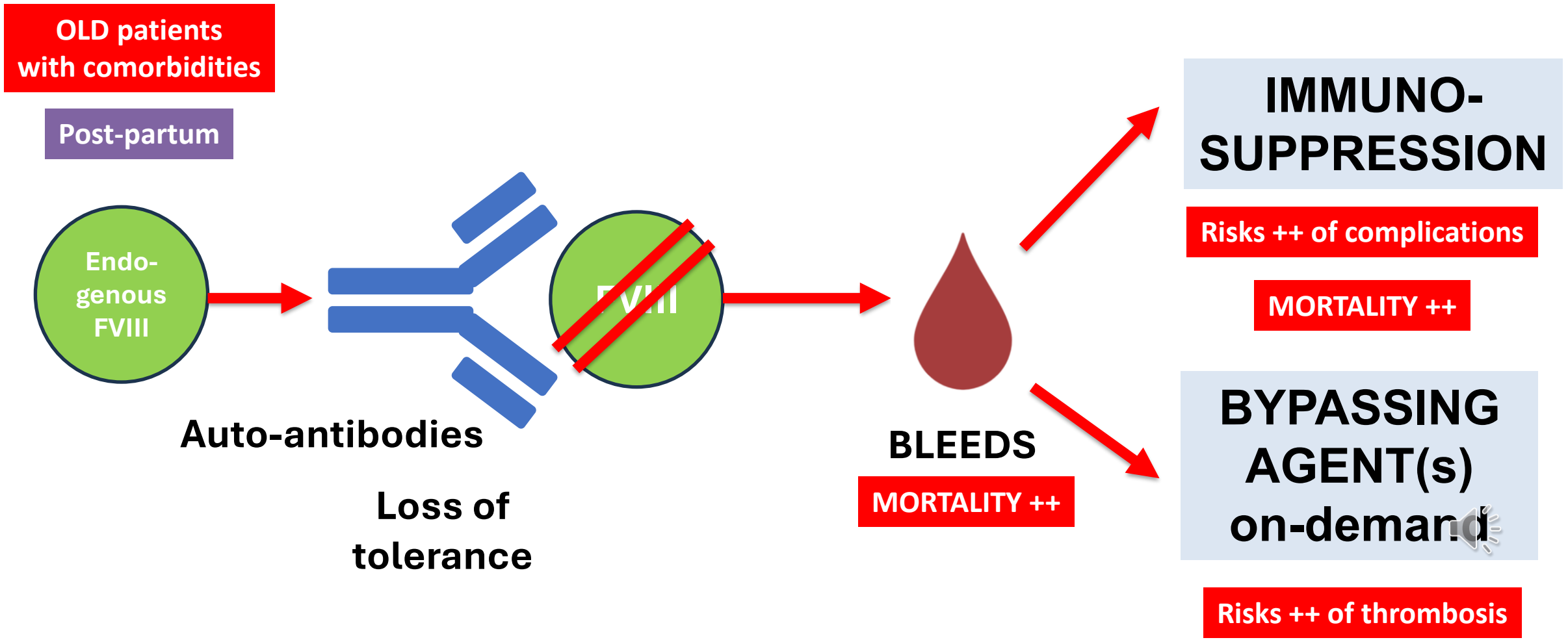




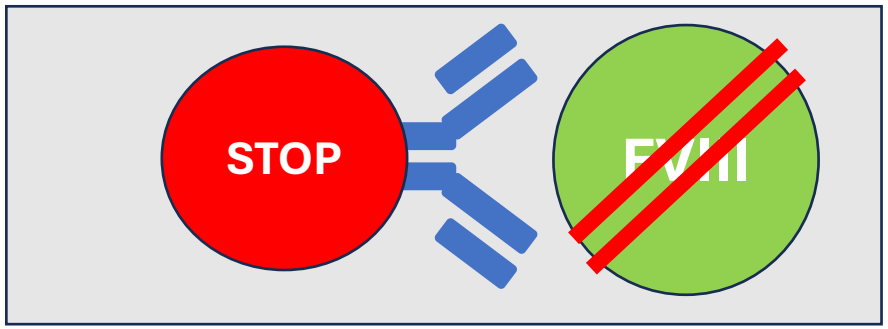




Pathophysiology and management of acquired Haemophilia A (AHA)



Management options for acquired HA

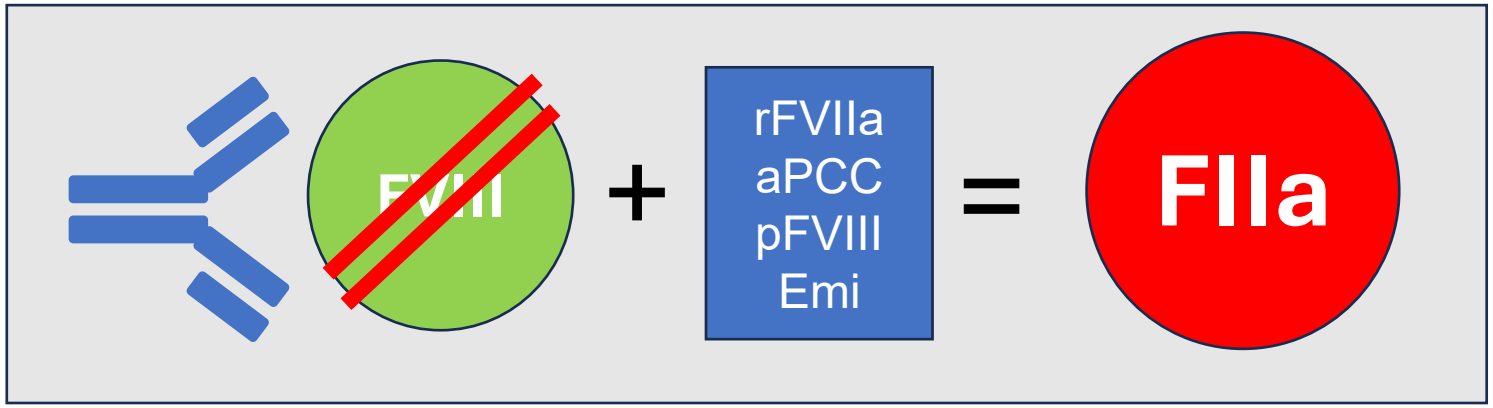


Immunosuppression

Glucocorticoid and
Cyclophosphamide
Rituximab

Alternative IST options (Limited data)

Bortezomib
Mycophenolate Mofetil
Tacrolimus
Azathioprine
Vincristine
Immune tolerance protocols

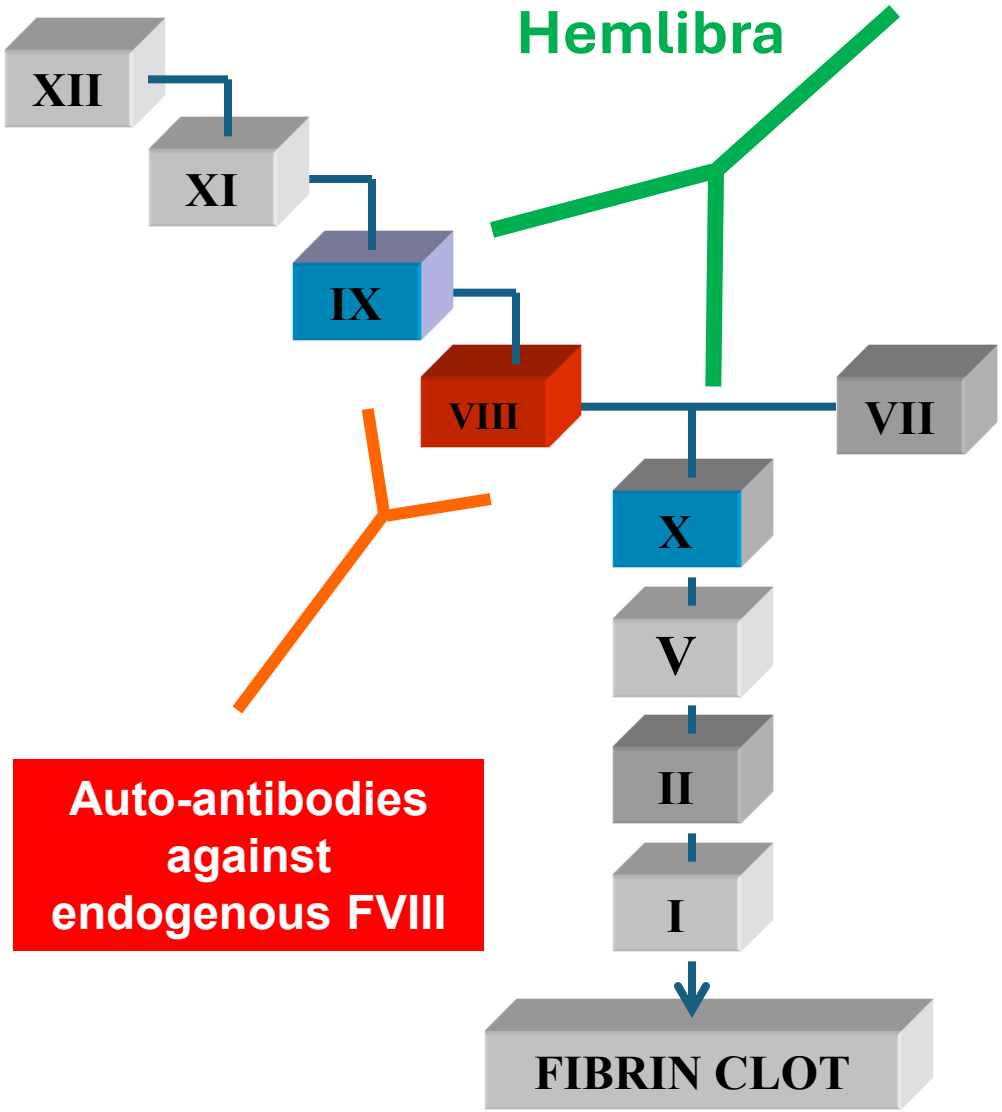


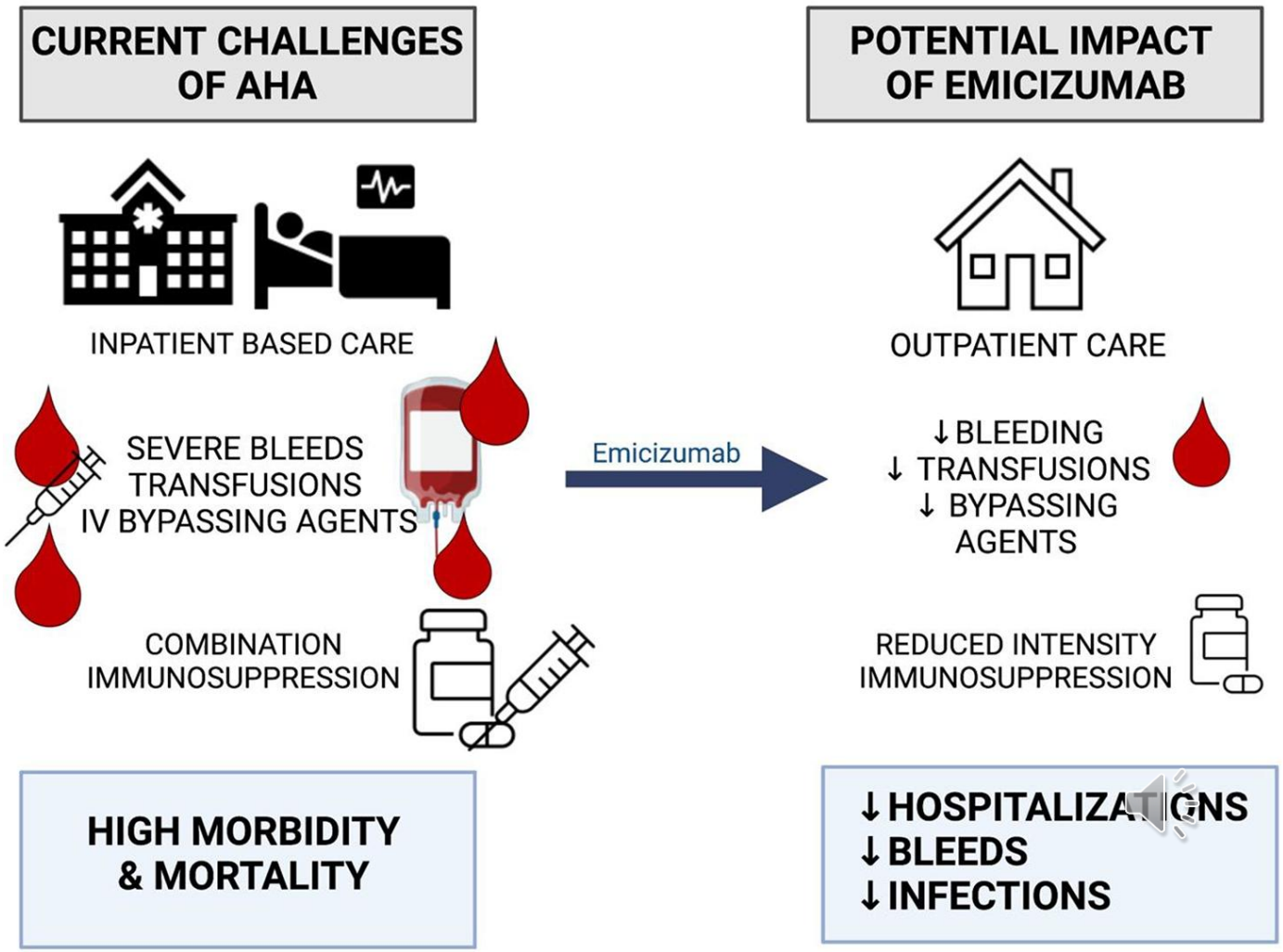
Haemostatic control

Recombinant Porcine FVIIII
Recombinant Factor VIIa
aPCC
Emicizumab (Off Label)

The Role of Emicizumab in Acquired Haemophilia A

Presenter: Rebecca Kruse-Jarres
Program: Education Program





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Isolated prolongation of the APTT

Sampling error / Interference

Lupus anticoagulant

anti-phospholipid syndrome (thrombosis)

FXII deficiency

No bleeding

Factor IX deficiency
Hemophilia B

FXI deficiency

FVIII deficiency
Hemophilia A
VWD (all types, 2N)



Female 72-year-old with bleeding after kidney surgery

- **No past history of bleeding symptoms**
- APTT, PT and TT : normal
- Fg : normal
- FVIII-FIX-FXI : normal
- PFA-100 : normal
- Platelet functional tests : normal
- Euglobulin Lysis Time : normal

Immune FXIII deficiency

Underlying lymhoma ?

- FXIII : not measurable
- Antibody against FXIII : + (14 Bethesda Units)
- **Patient presented with massive intracranial haemorrhage 48 hours after diagnosis and died**



Conclusions

- **Acquired coagulation disorders may complicate many haematological malignancies**
  - DIC
  - Acquired von willebrand disease
  - Coagulation factor defect of inhibitor
  - Hyperfibrinolysis
- **Coagulation disorders should be rapidly recognised and appropriate treatment initiated**



Bleeding disorders and haematological malignancies at a Glance

Players	Scenarios
Fibrinogen (FI)	Low – consumption (DIC) / defective production (Steroids / Asparaginase / interference with Abs
FVII	Low in very sick patients / Vitamin K deficiency / Liver disease
FX	Low in amyloidosis
FVIII	Low in acquired Hemophilia A
FV	Low if liver disease, DIC, rarely anti-FV auto-Abs
FXIII	Low in case of consumption / auto-Abs
VWF	Low in case of destruction (aortic stenosis, ECMO) or Abs (MM, MGUS, CLL,….)
FXII, FIX, FXI, FII	Rarely affected by haematological malignancies

Relevant blood tests

APTT	D-dimers
PT	Euglobulin Lysis Time
Fg	Clotting factors Assays
Thrombin Time	RoTEM
VWF:Ag and Ac	

Treatment options

Fresh Frozen Plasma
Clotting factor concentrates (Fg, ..)
Immunosuppression (…)
rFVIIa
Tranexamic acid



Suggested readings

- Disseminated Intravascular Coagulation in Hematologic Malignancies Semin Thromb Hemost. 2010 Jun;36(4):388-403. Franchini M, Di Minno MN, Coppola A.
- Pathogenesis and management of bleeding and thrombosis in plasma cell dyscrasias. Br J Haematol. 2009 Apr;145(2):151-63. Eby C.
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- Acquired von Willebrand syndrome: focused for hematologists. Haematologica. 2020 Aug;105(8):2032-2037. doi: 10.3324/haematol.2020.255117 . Massimo Franchini[1], Pier Mannuccio Mannucci[2]
- Acquired factor X deficiency in patients with amyloid light chain amyloidosis: incidence, bleeding manifestations, and response to high-dose chemotherapy. Blood. 2001 Mar 15;97(6):1885-7. Choufani EB, Sanchorawala V, Ernst T, Quillen K, Skinner M, Wright DG, Seldin DC.
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- Acquired Haemophilia A: A Review of What We Know. J Blood Med. 2022 Nov 23;13:691-710. doi: 10.2147/JBM.S342077. eCollection 2022. Mingot-Castellano ME, Rodríguez-Martorell FJ, Nuñez-Vázquez RJ, Marco P.



More references / open access

Acquired VWD

- https://haematologica.org/article/view/9977

Acquired Hemophilia

- https://www.jthjournal.org/article/S1538-7836(24)00648-2/abstract

Acquired bleeding diseases

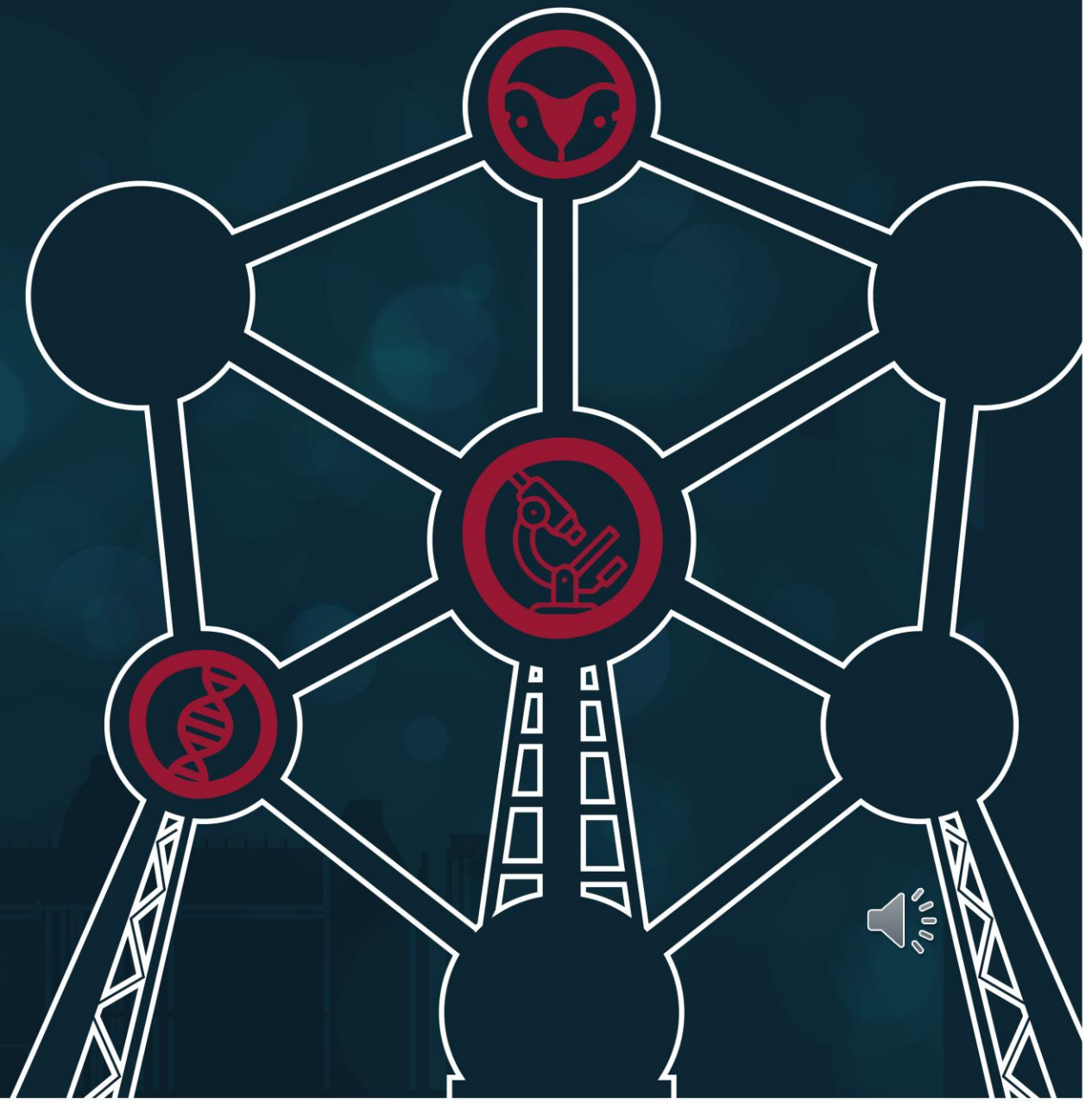
- https://onlinelibrary.wiley.com/doi/epdf/10.1111/hae.14995



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2027

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