Coagulation disorders

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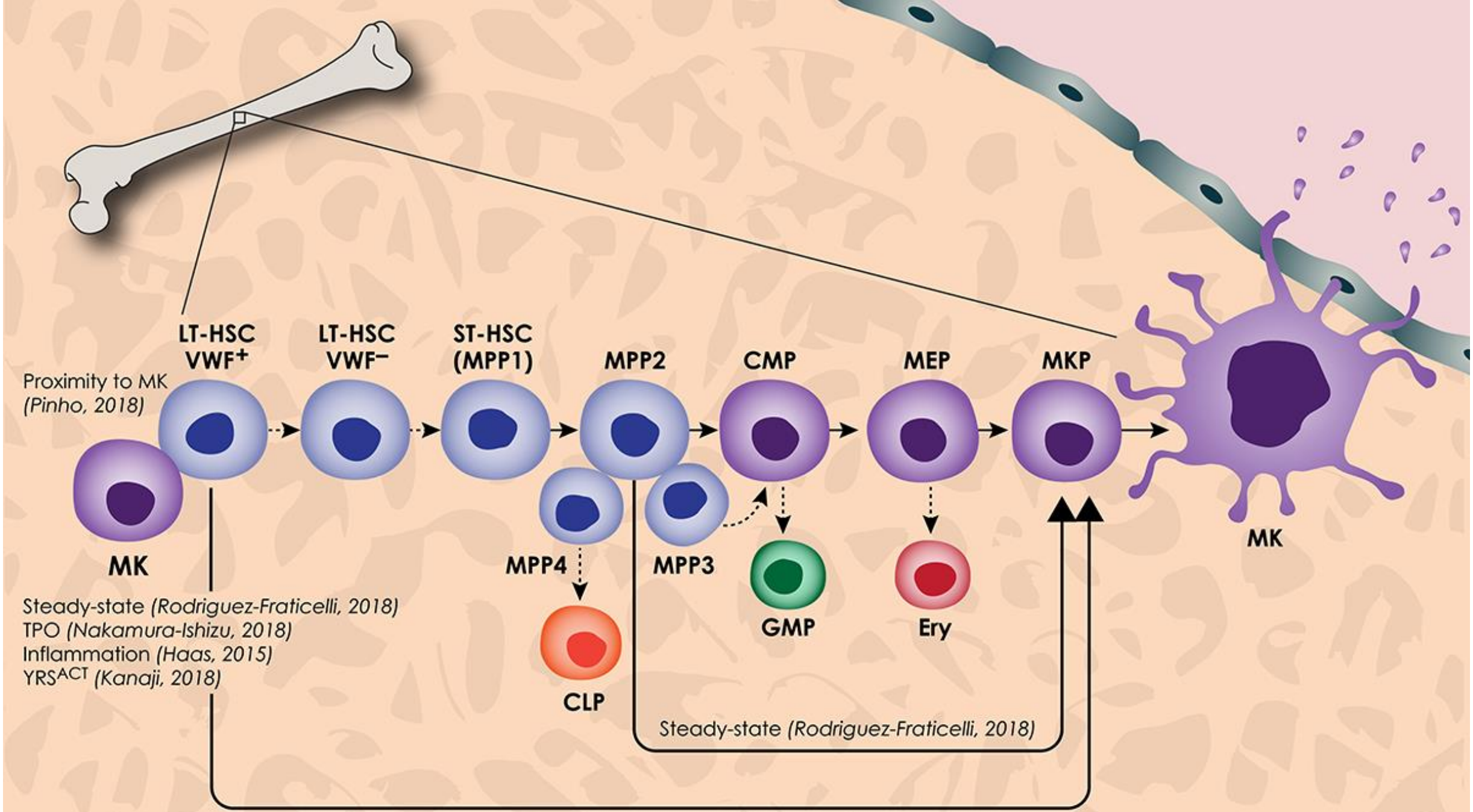
Physiology - repetition

- Haematopoietic stem cells (HSCs) -> multiple endomitoses -> megakaryocytes
- Factors
  - Thrombopoietin (TPO)
  - Transcription factors – RUNX1, GATA-1, -2, FLI-1, cascades – JAK2/STAT3/STAT5, MAPK/ERK, PI3K/Akt
- Important feature of megakaryocytes
  1. Creation of demarcation membrane system (DMS)
  2. ↑a- and dense granules + cytoplasmic expansion
  3. Dense tubular network + open canaliculi system -> granules release
- Bones sinusoids -> maturation into proplatelets -> circulation/lung vessels -> maturation into platelets

RUNX1 – runt-related transcription factor 1, FLI-1 – Friend leukaemia integration-1



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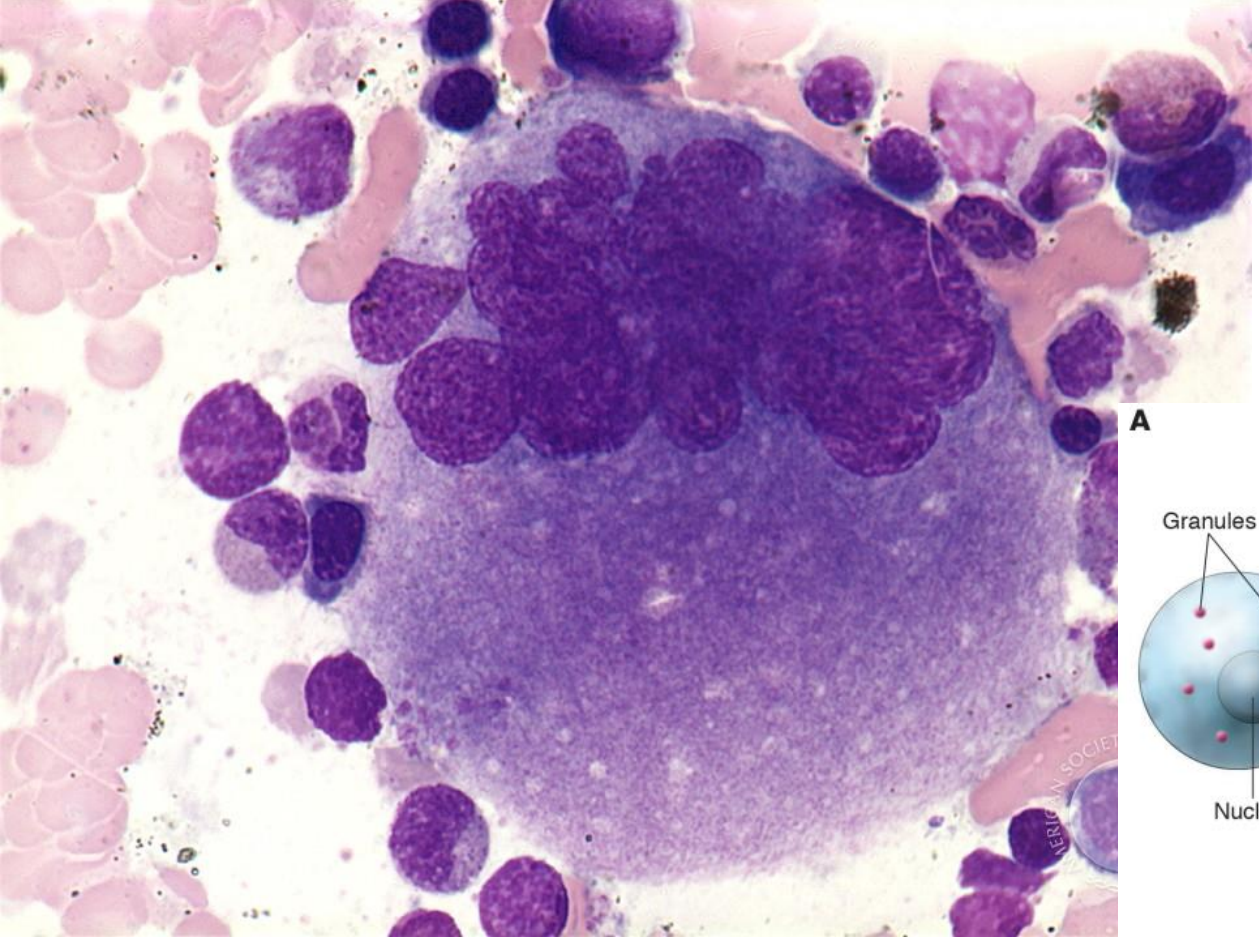

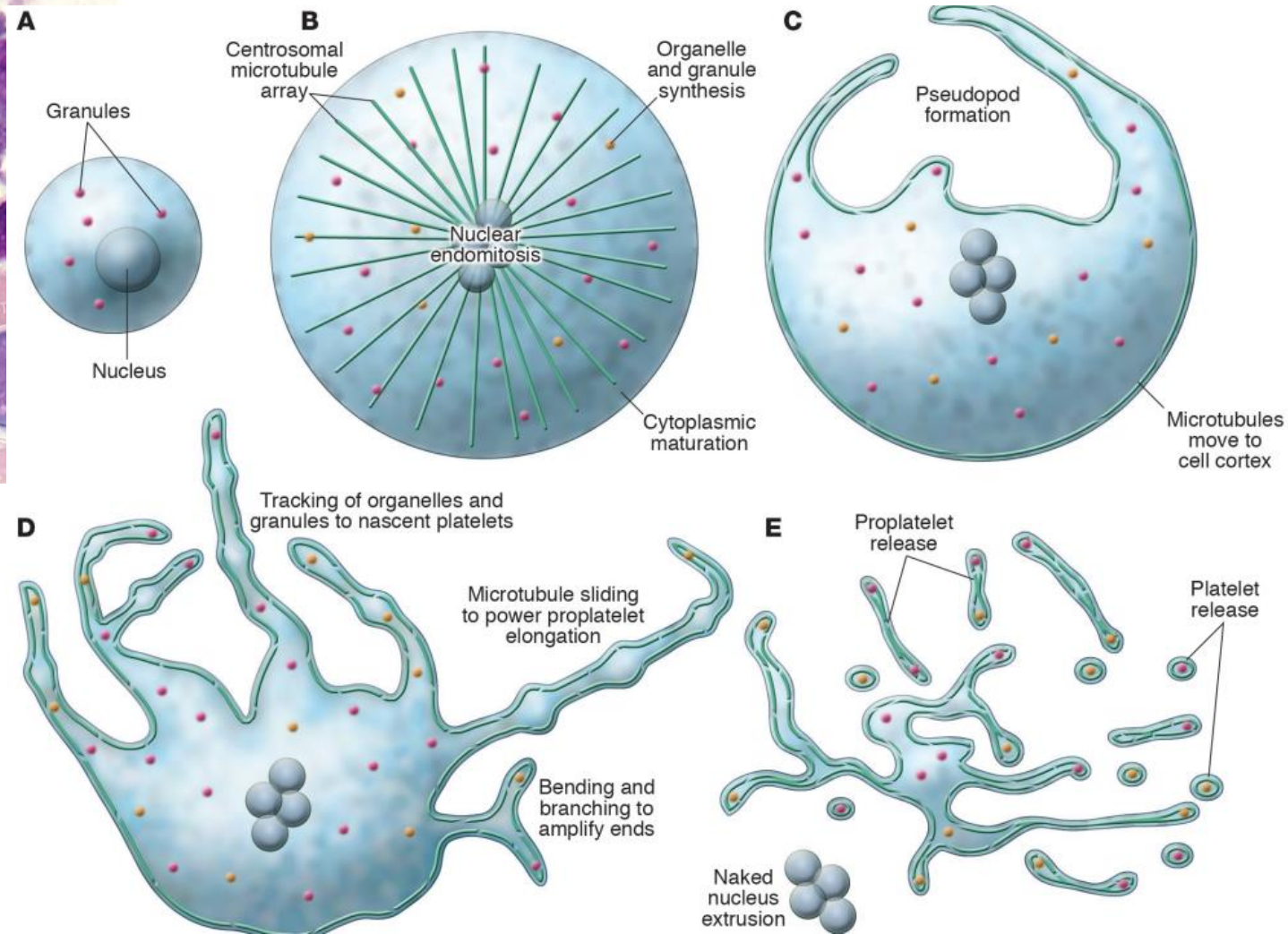

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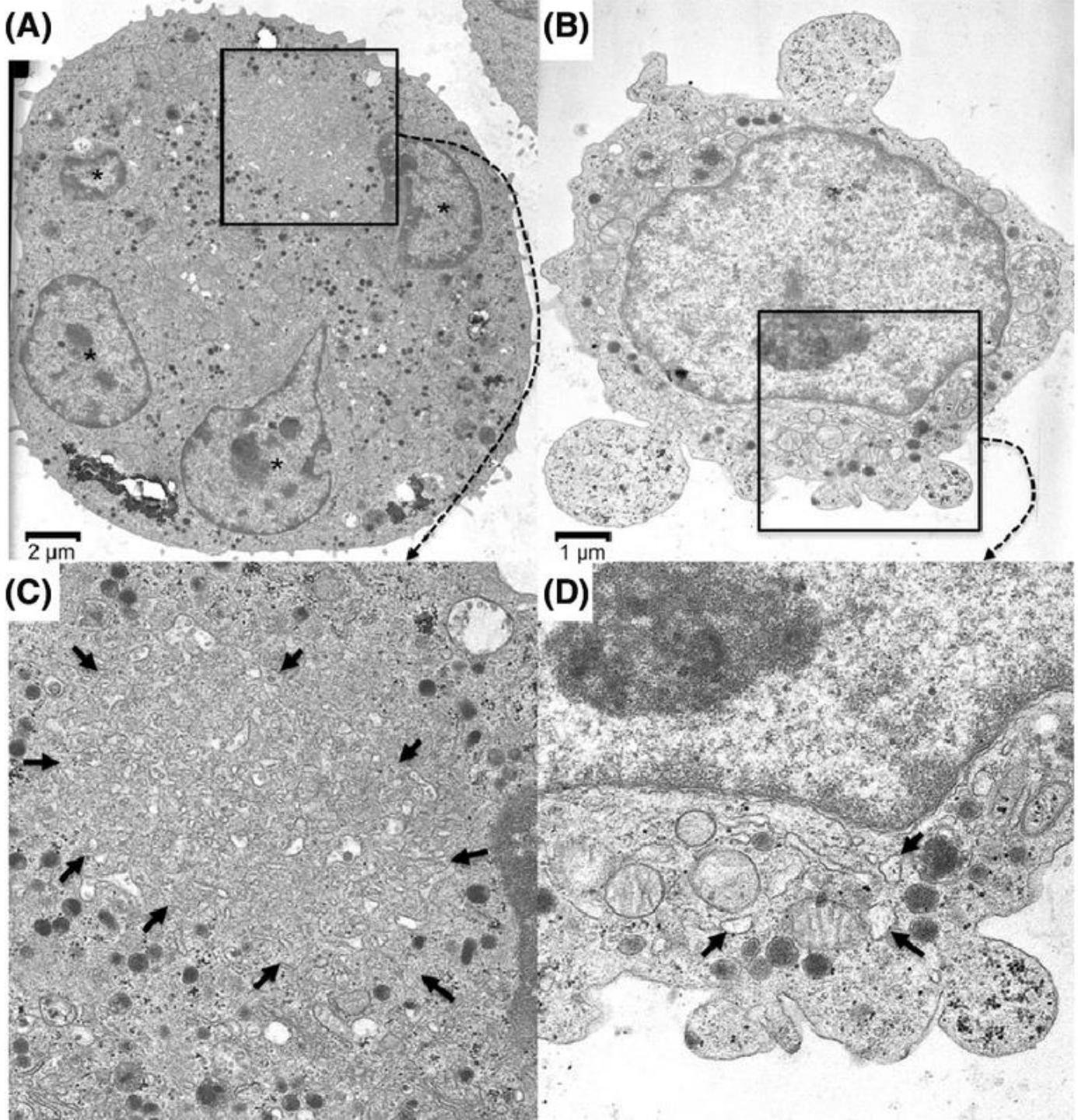

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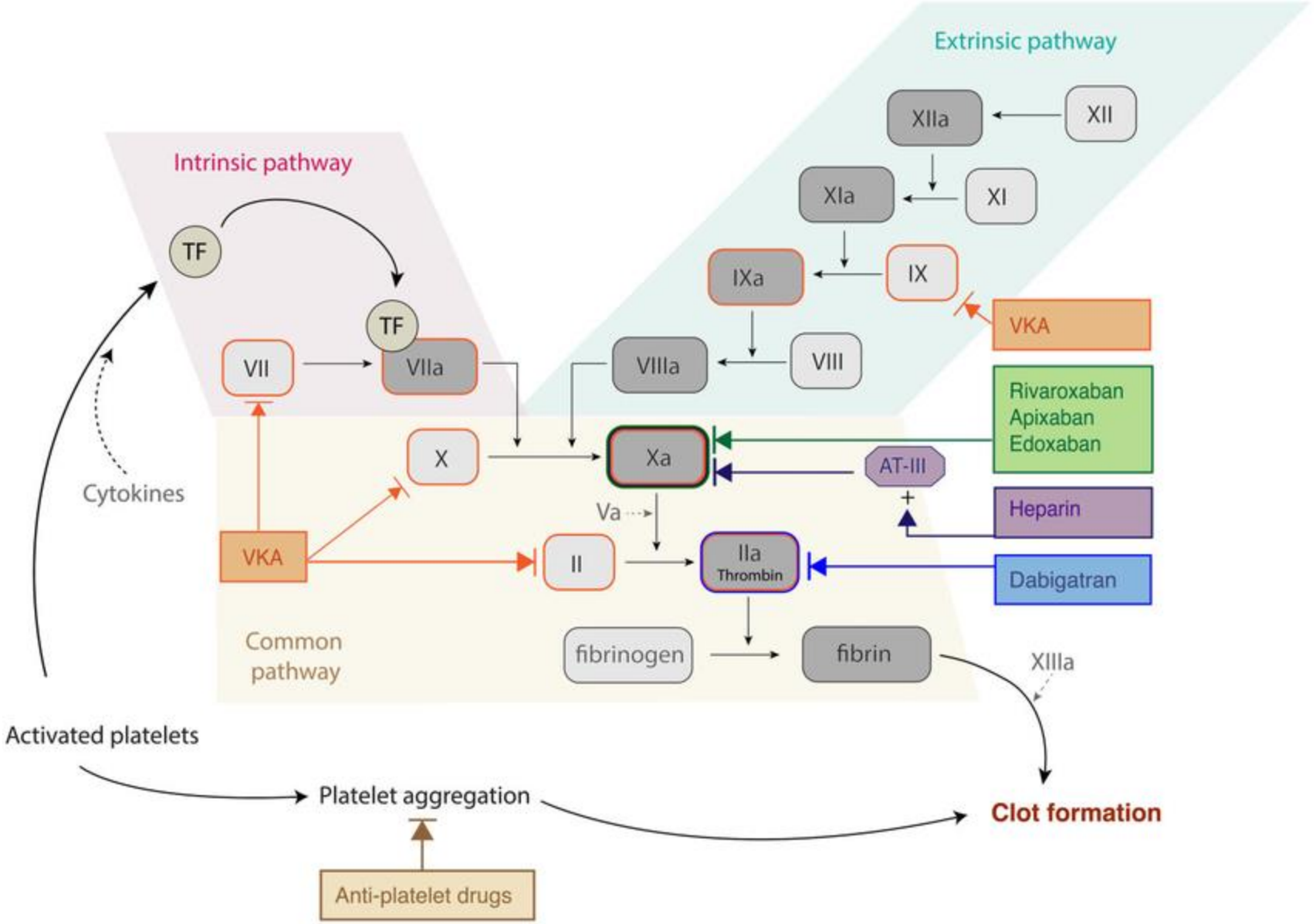
Coagulation cascade

- Three pathways
  1. Extrinsic
     - Trigger -> tissue damage -> tissue factor (FIII) exposed) -> activation of FVII -> complex FIII+FVIIa (+Ca^{2+}) -> FX activation
  2. Intrinsic
     - Trigger -> negative charge (damaged surfaces), HMWK, collagen, prekallikrein
     - Mechanism -> FXII to FXIIa -> FXI to FXIa -> FIX to FIXa -> FVIII to FVIIa (+Ca^{2+}) -> FX activation
  3. Common
     - FXa -> FII (prothrombin) to FIIa (thrombin) -> FI (fibrinogen) to Fia (fibrin) -> stable blood clot

COAGULATION IS NOT A LINEAR CASCADES AS IT INCLUDES PHASES OF AMPLIFICATION BY THROMBIN (FOR XI, VII, AND V)



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Secondary Hemostasis: *Coagulation Cascade*

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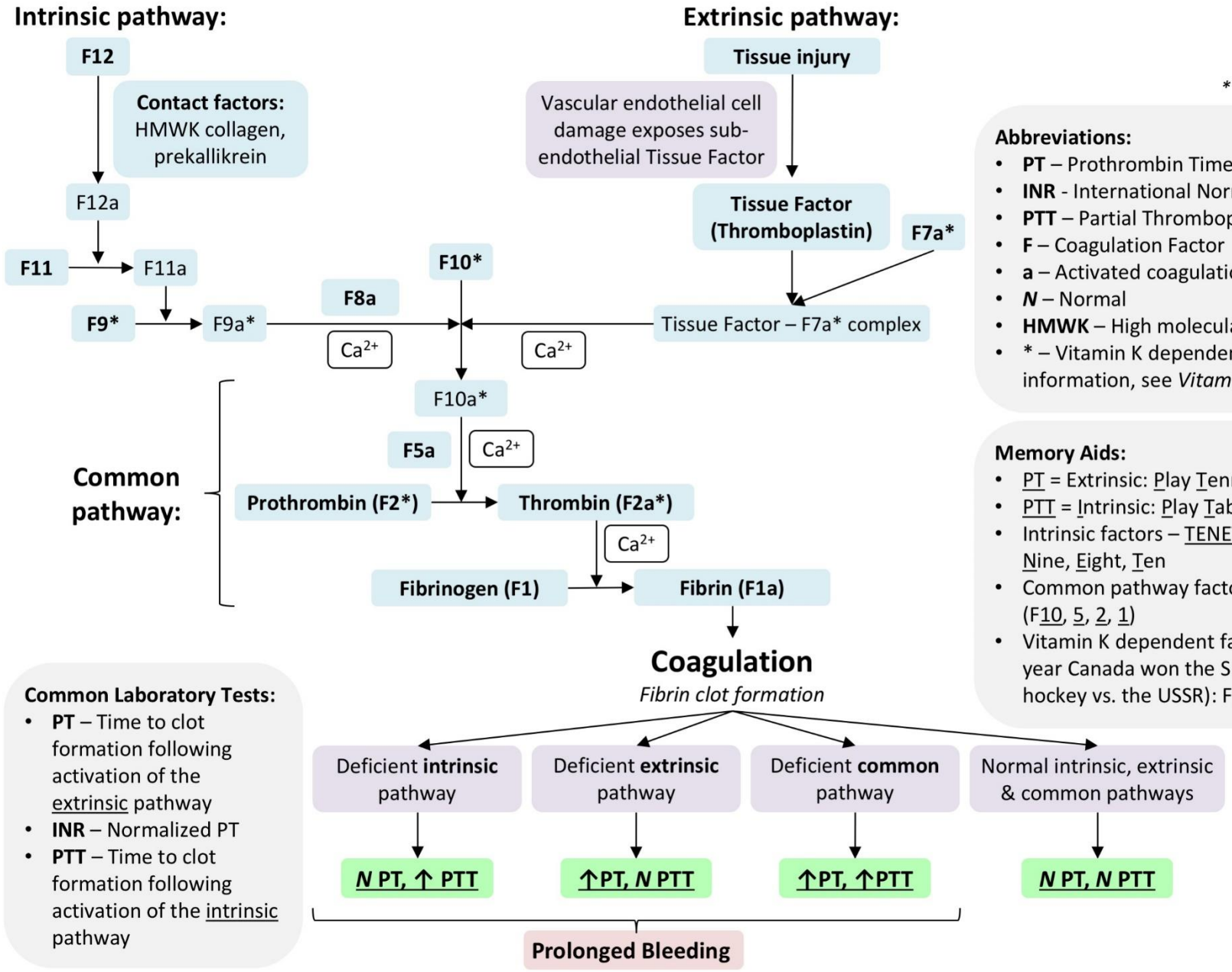


Abbreviations:
- **PT** – Prothrombin Time
- **INR** - International Normalized Ratio
- **PTT** – Partial Thromboplastin Time
- **F** – Coagulation Factor
- **a** – Activated coagulation factor
- ***N*** – Normal
- **HMWK** – High molecular weight kininogen
- * – Vitamin K dependent (for more information, see *Vitamin K Deficiency* slide)

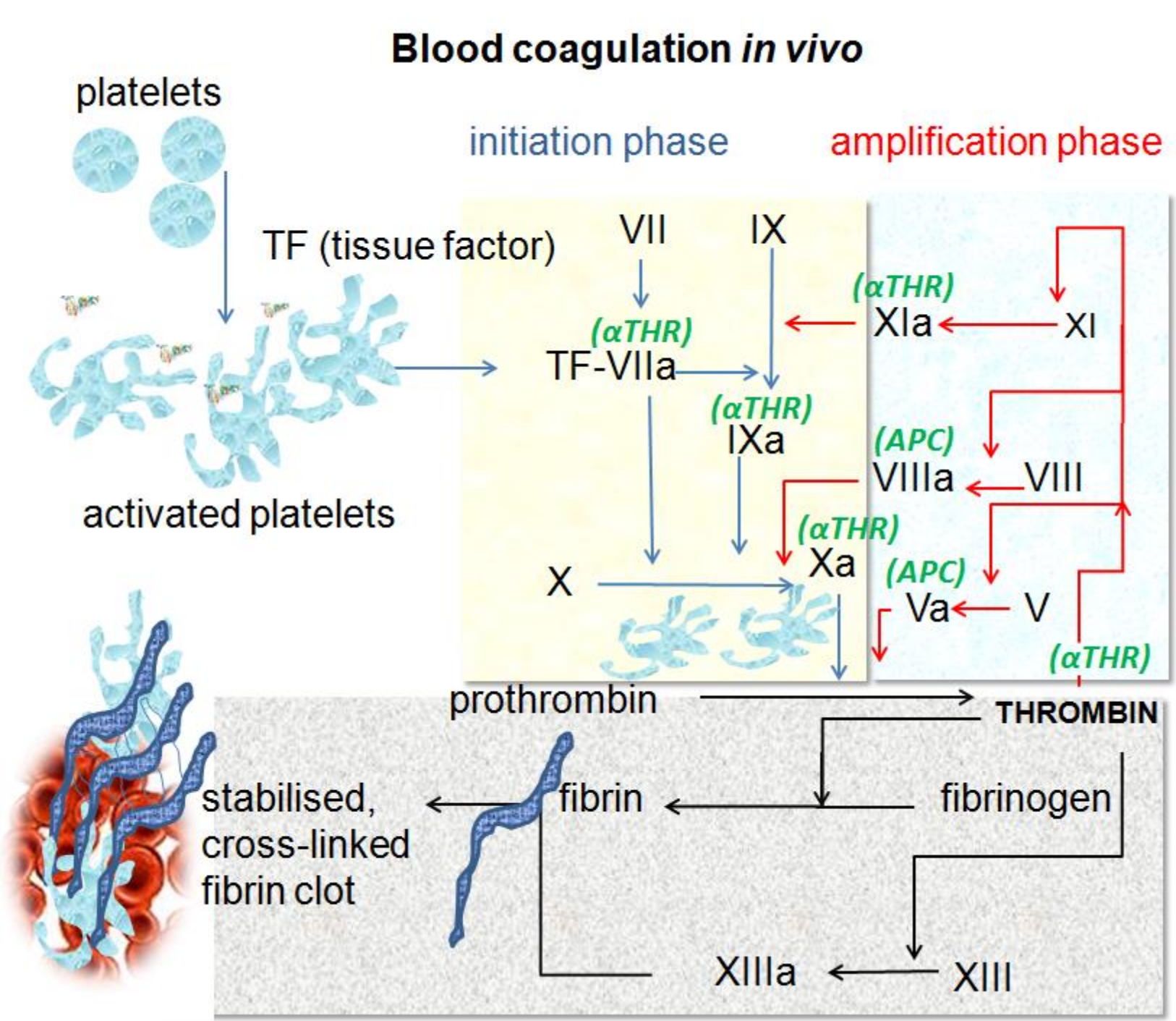
Memory Aids:
- PT = Extrinsic: Play Tennis outside
- PTT = Intrinsic: Play Table Tennis Inside
- Intrinsic factors – TENET: Twelve, Eleven, Nine, Eight, Ten
- Common pathway factors – 10/5=2, 2/2=1 (F10, 5, 2, 1)
- Vitamin K dependent factors – 1972 (the year Canada won the Summit Series in hockey vs. the USSR): F10, 9, 7, 2

Common Laboratory Tests:
- **PT** – Time to clot formation following activation of the extrinsic pathway
- **INR** – Normalized PT
- **PTT** – Time to clot formation following activation of the intrinsic pathway

Legend: Pathophysiology | Mechanism | Sign/Symptom/Lab Finding | Complications

Published **May 12, 2017** on www.thecalgaryguide.com

https://calgaryguide.ucalgary.ca/wp-content/uploads/2017/05/Secondary-Hemostasis-Coagulation-Cascade.jpg



COAGULATION IS NOT A LINEAR CASCADE AS IT INCLUDES PHASES OF AMPLIFICATION BY THROMBIN (FOR XI, VII, AND v)

https://upload.wikimedia.org/wikipedia/commons/4/4f/Coagulation_in_vivo.png

Some terms & parameters for repetition

- Primary haemostasis -> formation of a platelet plug
- Secondary haemostasis -> activation of a coagulation and formation of insoluble fibrin network
- Parameters
  - Platelets – 150,000 – 450,000 cells/μL
  - Prothrombin time (PT) – 11–13.5 seconds
  - INR (international normalised ratio) – 0.8-1.1
  - aPTT (activated partial thromboplastin time) – 25-35 seconds

Bleeding disorders

Thrombocytopenia

Thrombocytopenia (count)

- Peripheral blood platelets drop <50 000 cells/µl (factual <150 000 cells/µl)
- Causes
  1. Decreased production
     - Dehydration, vit. B9 and B12 deficiency
     - Leukaemia, myelodysplastic syndrome, aplastic anaemia
     - Liver failure -> ↓thrombopoetin
     - Sepsis, systemic viral/bacterial infection, leptospirosis
     - Congenital – e.g. Bernard-Soulier syndrome, Fanconi anaemia, Glanzmann thrombasthenia, May-Hegglin anomaly

Thrombocytopenia (count)

- Causes (continued)
  2. Increased destruction
     - Immune (idiopathic) thrombocytopenic purpura, thrombotic thrombocytopenic purpura, antiphospholipid syndrome, Dengue fever, Gaucher disease, Zika virus, DIC
  3. Drug induced
     - Valproate, methotrexate, carboplatin, interferon, isotretinoin, proton pump inhibitors
  4. Other
     - Laboratory error, snake poison, Lyme disease, thrombocytapheresis, Niemann-Pick disease

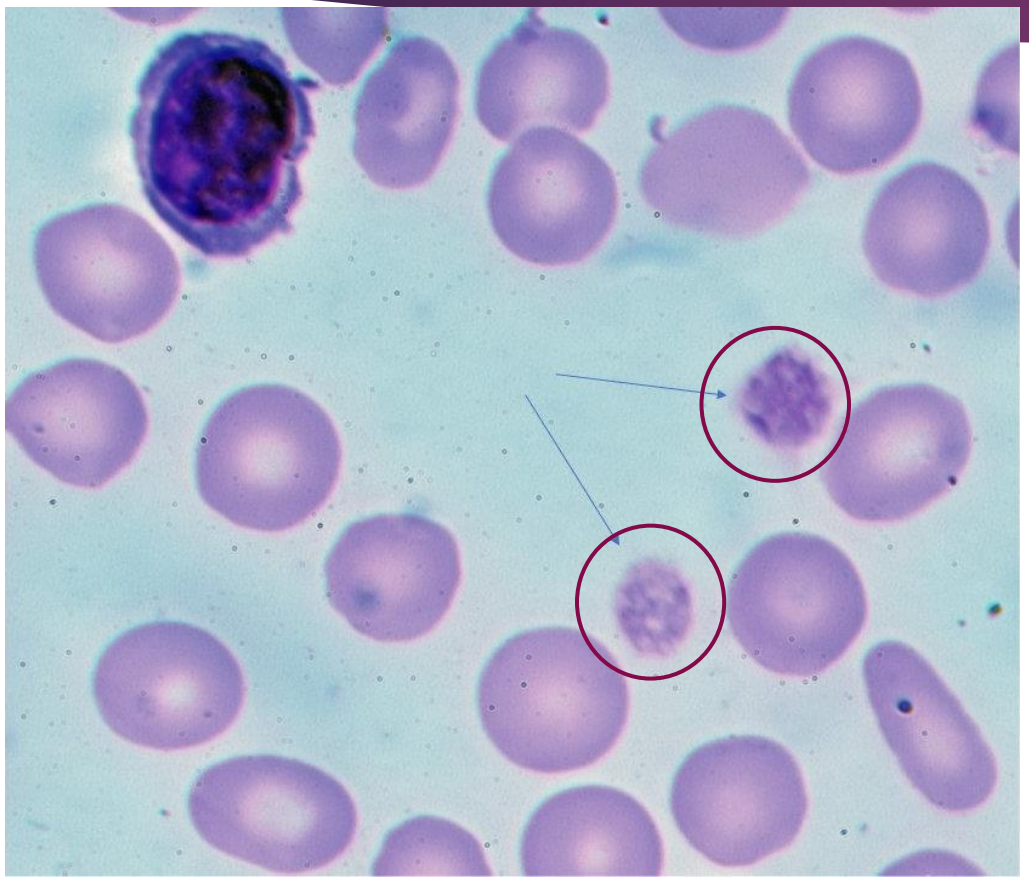
Idiopathic/immune thrombocytopenic purpura

- Autoimmune disease typical with decreased platelet counts and haemostasis disorders in absence of other causes
- Forms
  - Acute – children mostly, after viral infections
  - Chronic – adults mostly, unclear mechanism
- Pathomechanism
  - ? -> IgG against glycoprotein IIb-IIIa or Ib-IX -> Tr opsonisation -> Tr retained by macrophages (spleen) and Liver (Kuepfer cells)
  - Antibodies damaging megakaryocytes, decreased thrombopoietin production (possible T-cells hyperactivity)

Idiopathic thrombocytopenic purpura

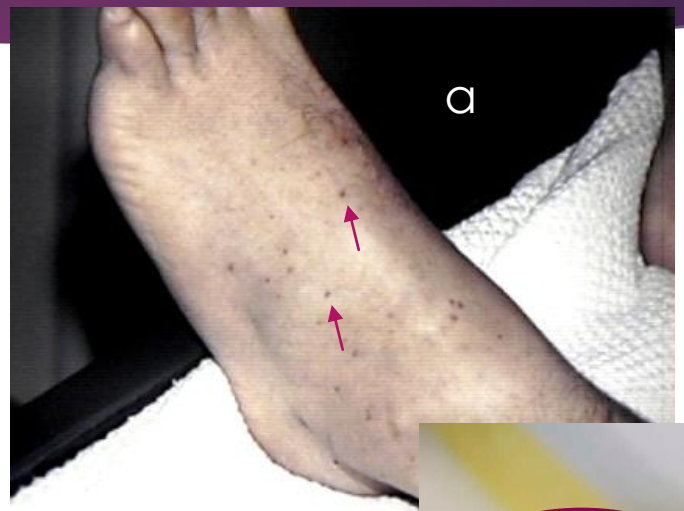
- Manifestations
  - Tr <50 000 cells/μl – petechial and purpuras
  - Tr <20 000 cells/μl – epistaxis, mouth bleeding, menorrhagia
  - Tr <10 000 cells/μl – spontaneous hematoma emerging (oral cavity, mucosa), prolonged bleeding time in bruises and small wounds
  - Tr <5 000 cells/μl – spontaneous subarachnoid/intracerebral bleeding, abnormal GIT blood loss, internal bleeding
- Prognosis
  - Good, only small patients percentage experience a fatal bleeding episode

Idiopathic thrombocytopenic purpura



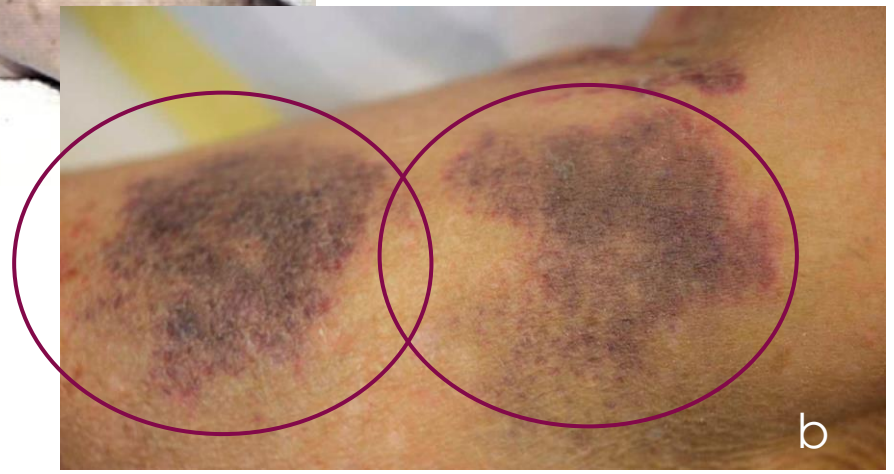
Macrothrombocytes (Giemsa method)

https://upload.wikimedia.org/wikipedia/commons/9/9a/Giant_platelets_in_ITP.jpg



<- Petechia

Purpuras ->



https://upload.wikimedia.org/wikipedia/commons/1/13/Petechiaesmall.jpg

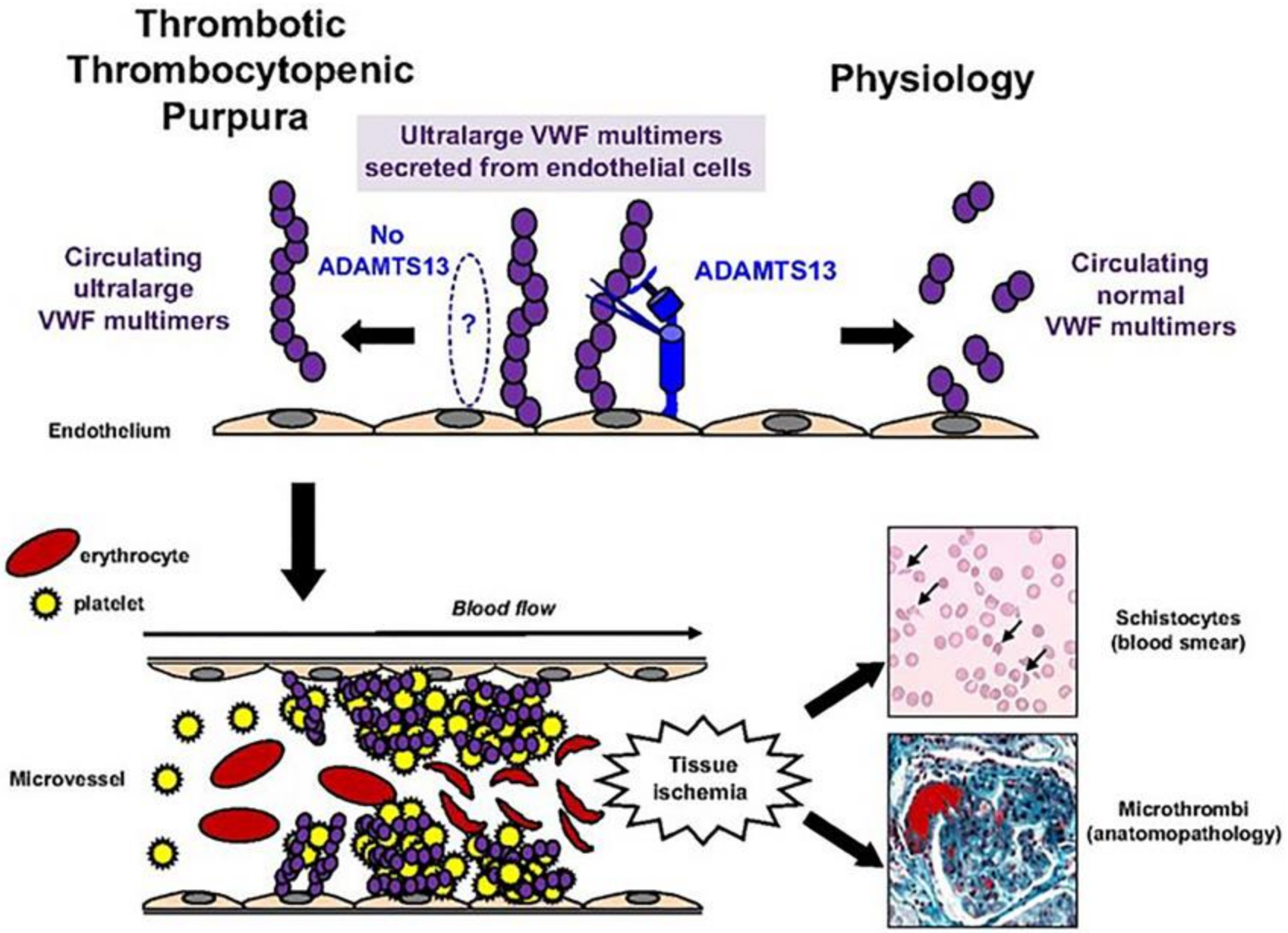
https://media.post.rvohealth.io/wp-content/uploads/sites/3/2022/12/purpura-skin-slide1.jpg

Thrombotic thrombocytopenic purpura

- Definition – clots formation in microvasculature leading to platelets consumption and thus bleeding manifestations due to thrombocytopenia
- Causes
  - Acquired -> autoAb against ADAMST13 (von-Willebrand factor cleaving-protease)
  - Genetics -> Upshaw-Schulman syndrome (deficiency/dysfunction of ADAMST13 – inherited (autosomal recessive)
- Prevalence (worldwide, 2024)
  - Idiopathic – 1/165,000-1/1,000,000
  - Congenital – 1/60,000-1/2,500,000

Thrombotic thrombocytopenic purpura

- Mechanism
  - Improper cleaving of vWF multimers -> acceleration of coagulation -> low platelets
  - Often leading to haemolytic anaemia manifestation -> red blood cells caught in the clot and exposed to shear stress
- Symptoms
  - Fever
  - Psychic alteration
  - Low platelets (often <30,000/cells/µL) -> bruises, petechiae
  - Reduced kidney function
  - Signs of microangiopathic haemolytic anaemia (schistocytes)



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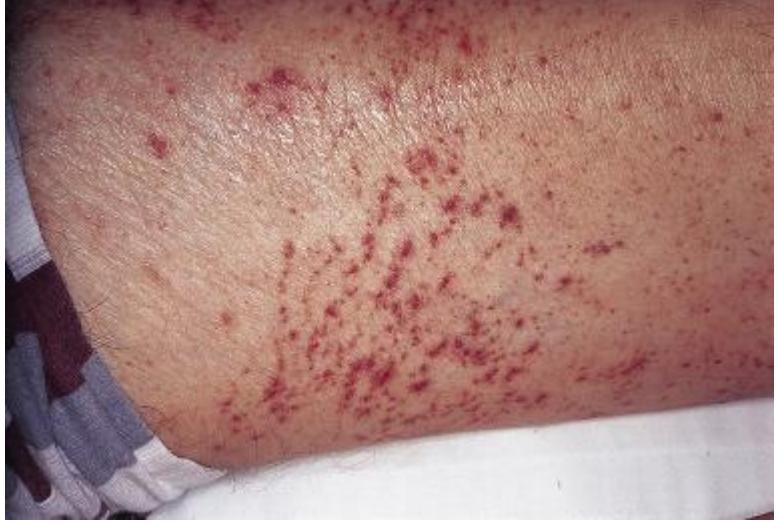
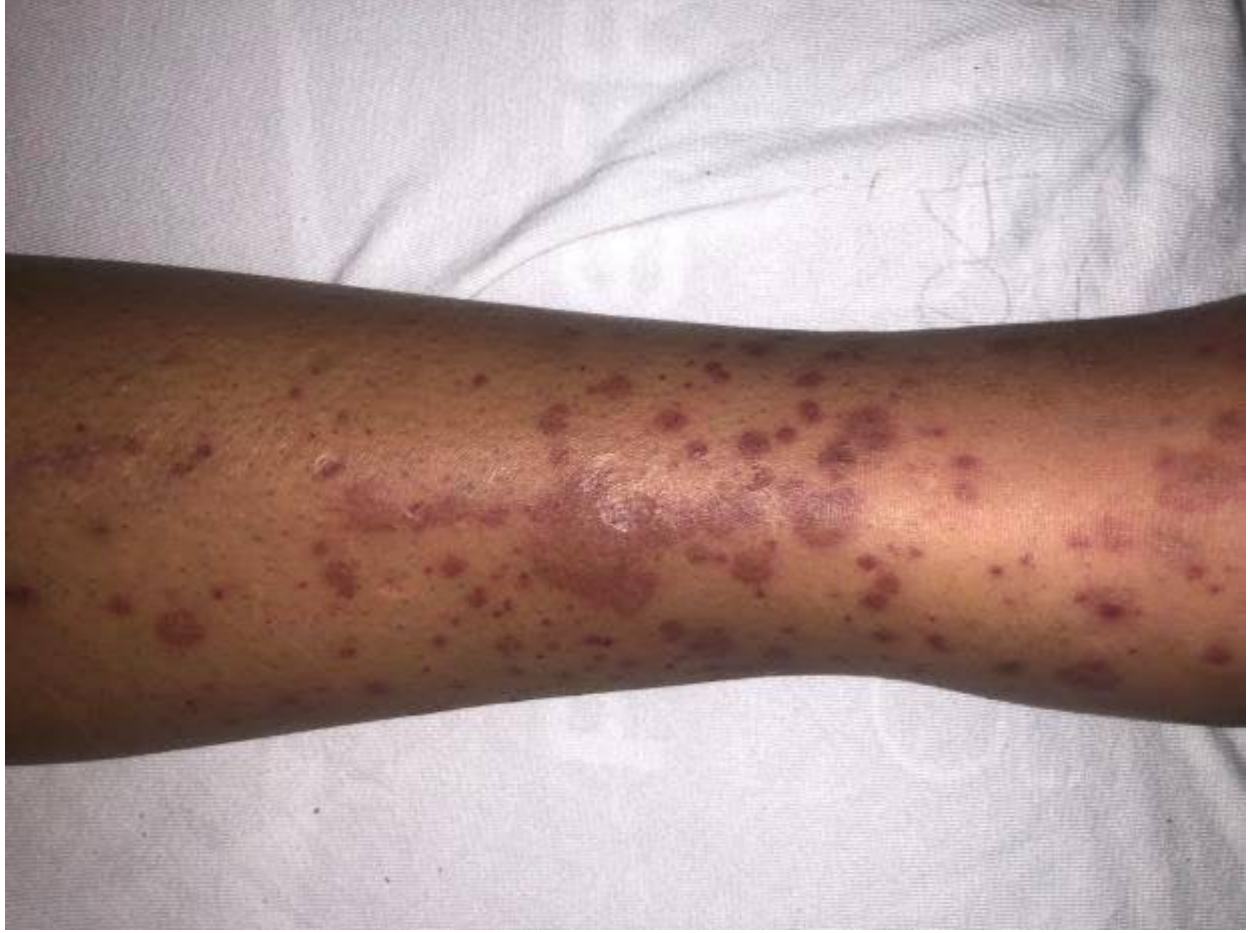
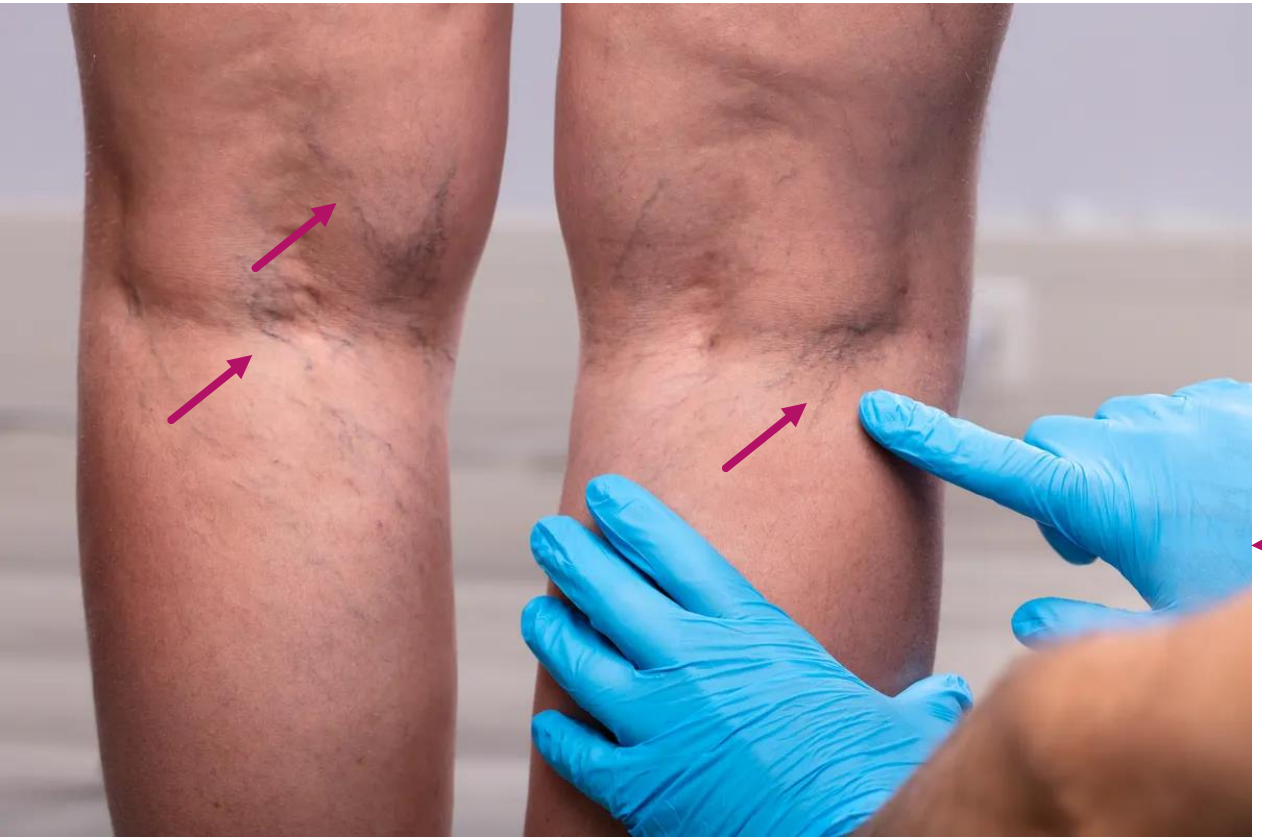


Petechia (above)



Purpura (above)



Multiple thrombi in microcirculation (purple arrows)

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https://www.humanizacjamedycyny.pl/wp-content/uploads/2024/03/zakrzepica.webp

Differences among ITP, TTP and DIC

Parameter	ITP	TTP	DIC
Pathogenesis	Antibodies production	Endothelial defect	Thrombin excess
Clinical condition	Not sick	**Sick**	**Sick**
Red cells	Normal	**Schistocytes**	**Schistocytes**
PT (INR)	Normal	Normal/Mild elevation	**Increased**
(a)PTT	Normal	Normal/Mild elevation	**Increased**
Fibrinogen	Normal	Normal	**Decreased**
Fibrinogen degradation	Normal	Normal/Mild increase	**Increased**
D-dimers	Normal	Normal/Mild increase	**Increased**
Management	Supportive Steroids IVIG, Splenectomy	Supportive Plasma exchange Steroids	Supportive

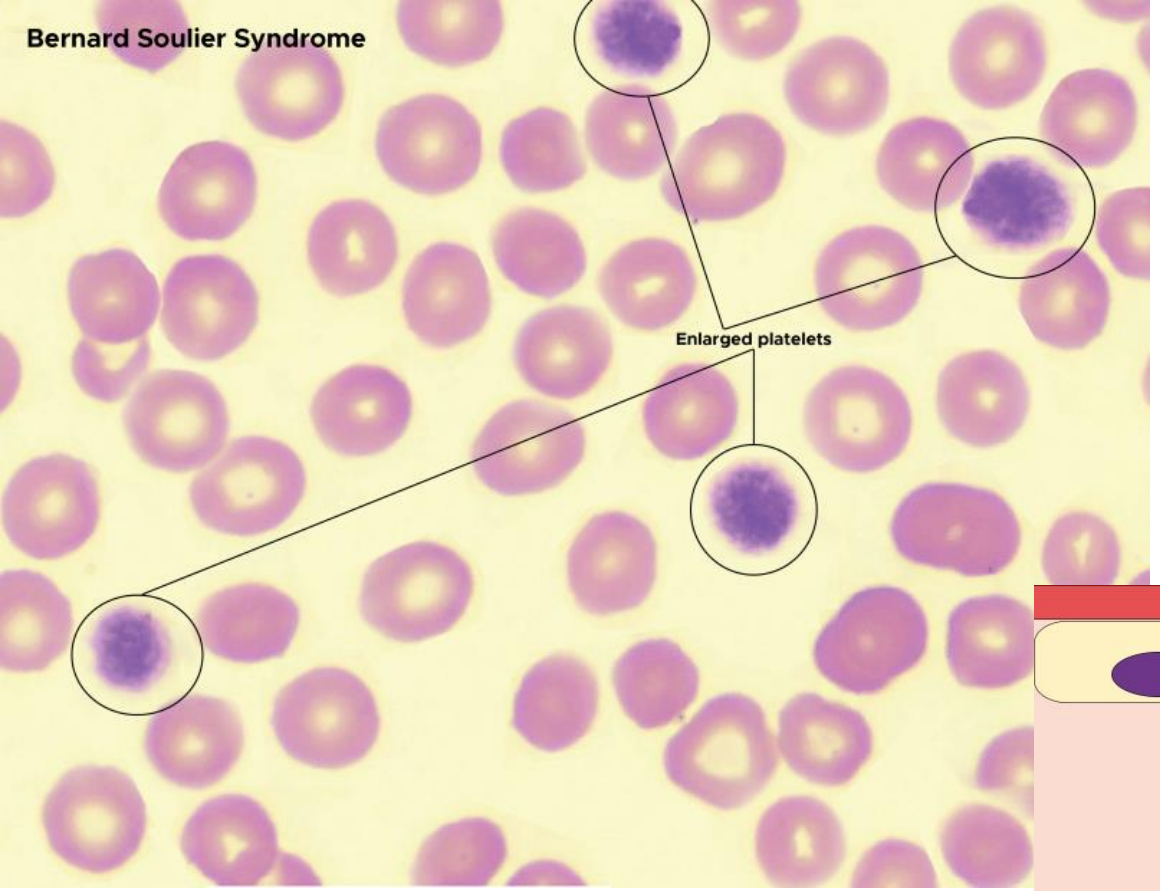
Thrombocytopathies

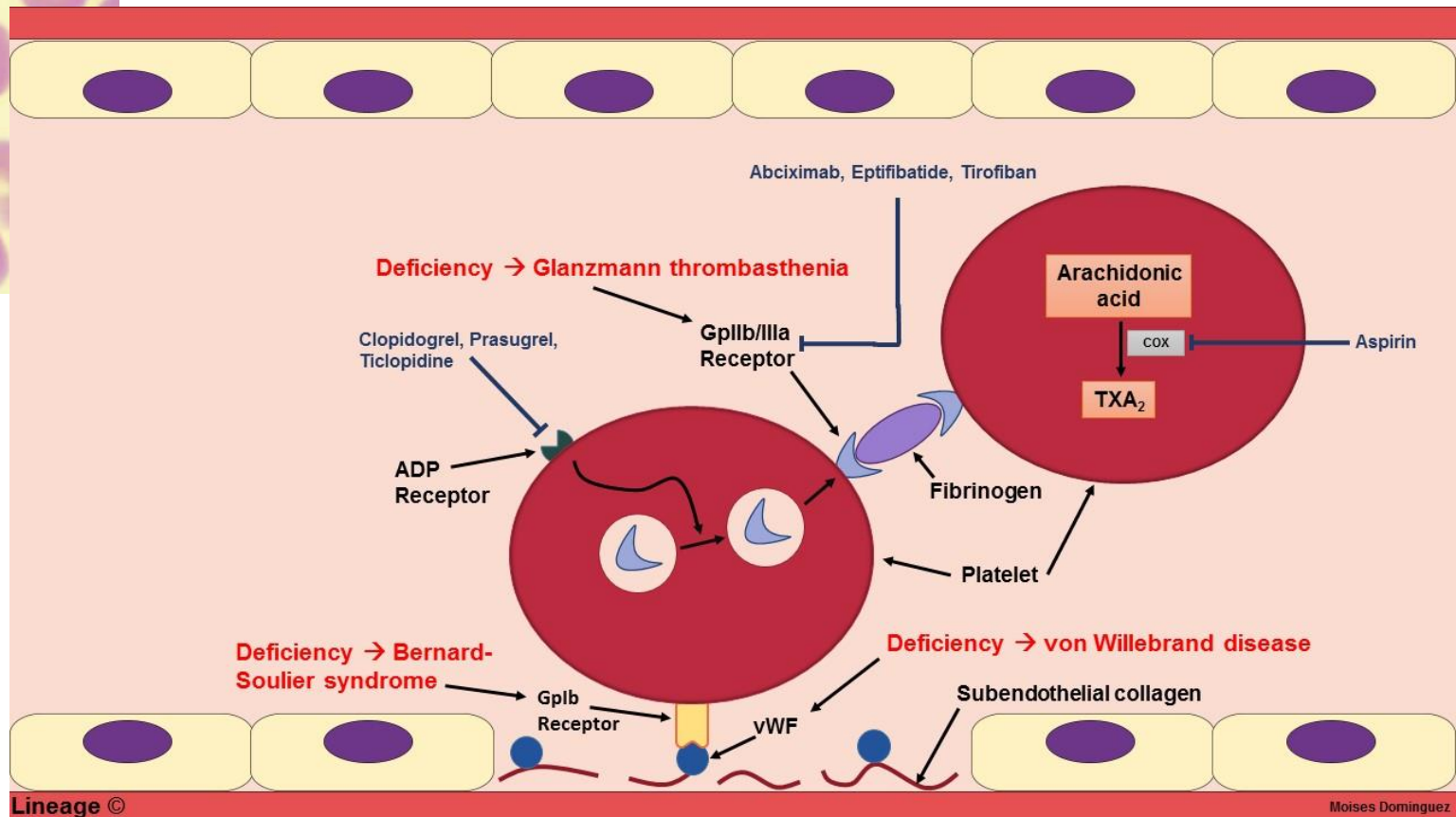
Thrombocytopathies (function disorder)

- Platelets functions disorder, platelets count may or may not be decreased
- Causes
  1. Congenital
     - Adhesion disorders – Bernard-Soulier syndrome
     - Activation disorders – Hermansky-Pudlak syndrome, grey platelets syndrome
     - Aggregation disorders – Glanzmann thrombasthenia, Wiskott-Aldrich syndrome
     - Coagulation activity disorders – Scott syndrome
  2. Acquired
     - Paroxysmal nocturnal haemoglobinuria, asthma, aspirin, tumours, malaria...

Bernard-Soulier syndrome

- Definition – a rare bleeding disorder caused by deficiency in glycoprotein Ib-IX-V complex -> improper binding to vWF factor
- Pattern – autosomal recessive
  - Mutation in genes GPB1A, GPB1B a GP9
- Gender – both
- Epidemiology - <1:1,000,000 (worldwide, 2024)
- Manifestations
  - Perioperative and postoperative bleeding
  - Bleeding gums, bruising, epistaxis, hyper- and dysmenorrhoea
  - Large platelets in circulation





https://www.ncbi.nlm.nih.gov/books/NBK557671/bin/Bernard__Soulier__Syndrome.jpg
https://upload.medbullets.com/topic/111017/images/platelet%20aggregation.jpg

Glanzmann thrombastenia

- Definition – a rare bleeding disorder caused by deficient quality or quantity of glycoprotein IIb/IIIa (receptor for fibrinogen)
- Pattern – autosomal recessive
- Gender – both
- Prevalence – 1:1,000,000 (2023); higher in consanguine marriages regions (up to 1:200,000)
- Manifestation
  - Gingival bleeding, nosebleeds, hypermenorrhoea, postpartum and postoperative bleeding
  - Platelet aggregation normal with ristocetin, but abnormal with ADP, thrombin, collagen or epinephrin

Common Symptoms of Glanzmann Thrombasthenia

Epistaxis (Nosebleeds)

Gingival bleeding (Gum bleeding)

Bruising (Ecchymoses)

Petechiae

Prolonged bleeding from minor cuts

Menorrhagia (Heavy menstrual bleeding)

myhematology.com

https://b779364.smushcdn.com/779364/wp-content/uploads/2025/05/Glanzmann-Thrombasthenia-Symptoms.jpg?lossy=2&strip=1&webp=1

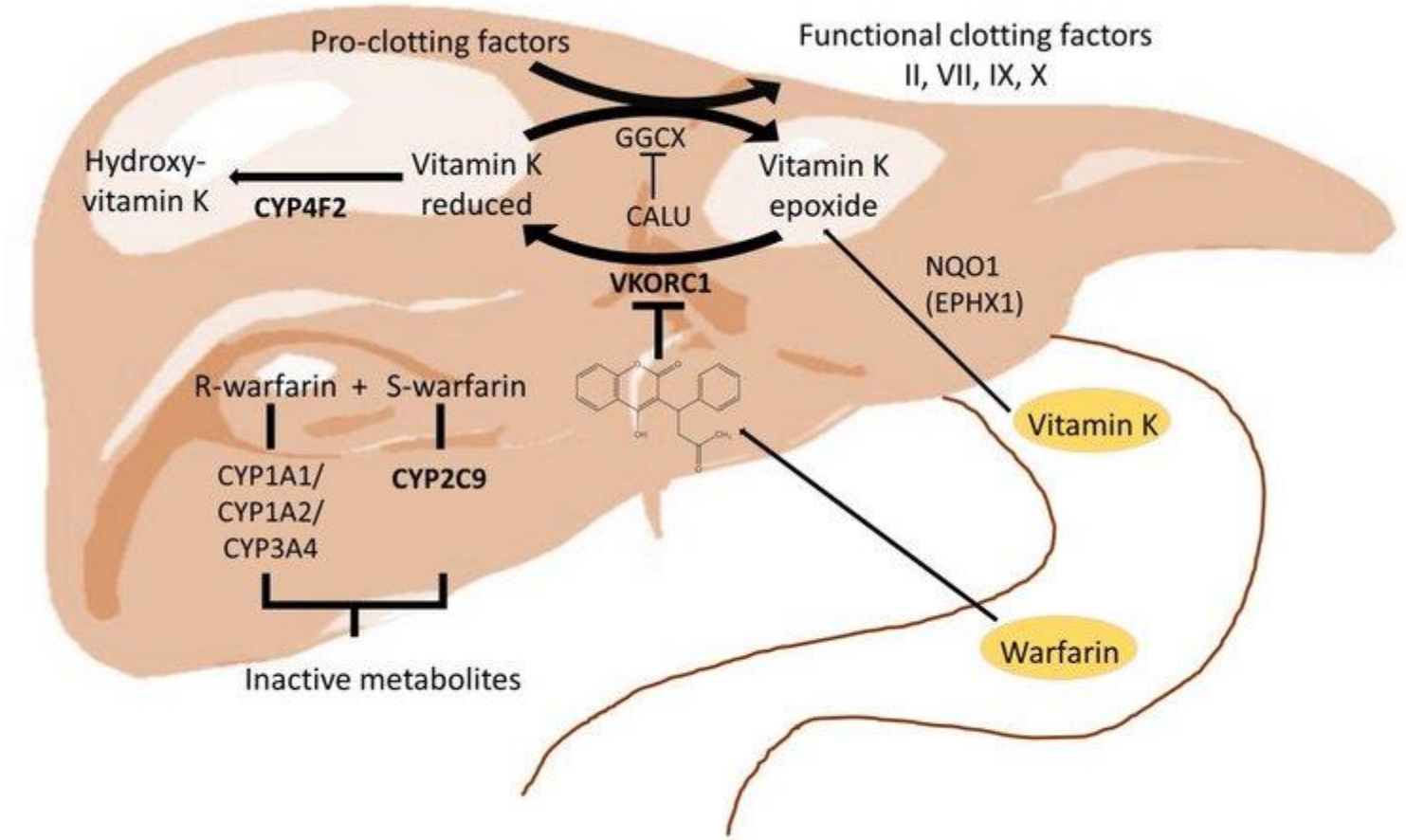
Aspirin-induced thrombocytopathy

- Aspirin (acetylsalicylic acid) -> cyclooxygenase blocked
  - Platelets prostaglandins synthesis decreased
- ADP production inhibited, also platelets reaction to granules release after collagen exposure
- Aspirin does not decrease platelets count!

- Aspirin may induce auto-antibodies production – auto-anti-gp-IIb/IIIa, auto-anti-gp-Ia/IIa -> increased platelets destruction -> thrombocytopenia

Warfarin

- Definition – an anticoagulant drug used in prevention of venous thrombosis, thromboembolic events, myocardial infarction and atrial fibrillation
- Mechanism
  - Inhibition of vitamin K epoxide reductase subunit 1
    - Reduced supplies of functional vitamin K
- Factors affected
  - ↓vitamin K-dependent factors -> FII, FVII, FIX, and FX
  - ↓vitamin K-dependent regulatory proteins -> protein C, and protein S



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American Dental Association recommendation in anticoagulative therapy

- If the INR is within therapeutical range (1.5-3.0) no discontinuation of therapy is advised
  - Risk of therapy discontinuation are higher than bleeding risk during the procedure
- INR <3.5 is considered safe (some sources state even <4.0)
- Drugs considered to be safe (in stated ratios)
  - Warfarin*
  - Antiplatelet drugs* – mono/dual-therapy – aspirin, clopidogrel, ticlopidine, prasugrel, ticagrelor
  - Direct-acting oral anticoagulants** – dabigatran, rivaroxaban, apixaban, edoxaban

* - strong evidence, ** - limited evidence

Coagulopathies

HAEMOPHILIA A, B, AND C

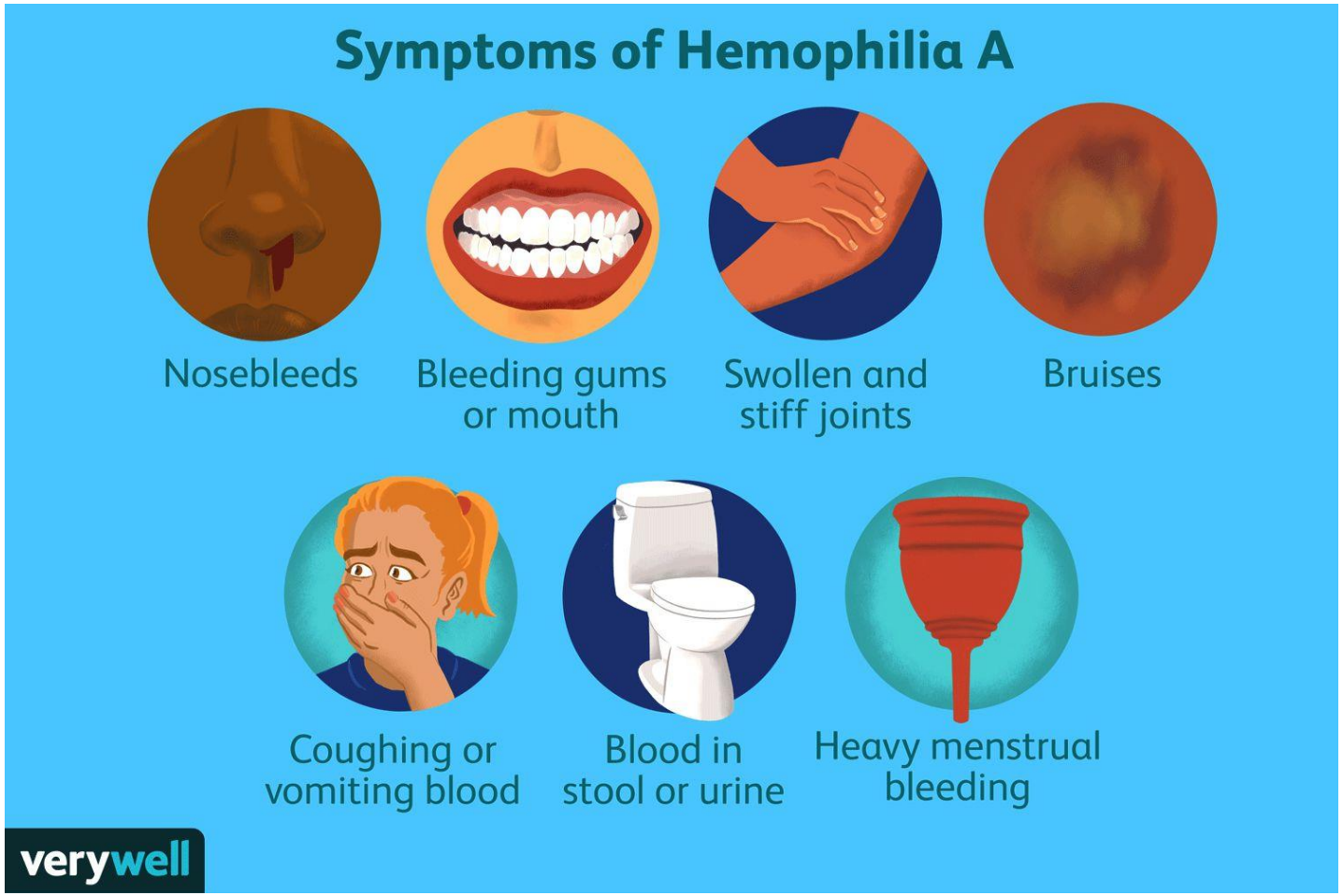
VON WILLEBRAND DISEASE

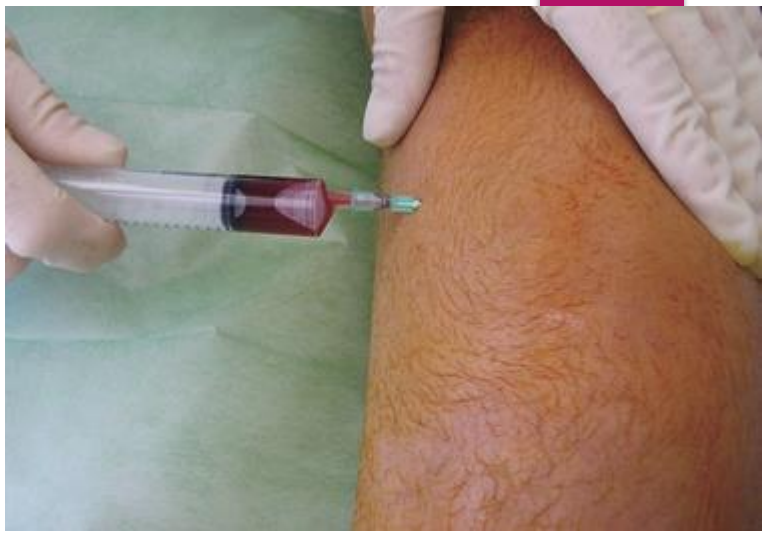
Haemophilia A

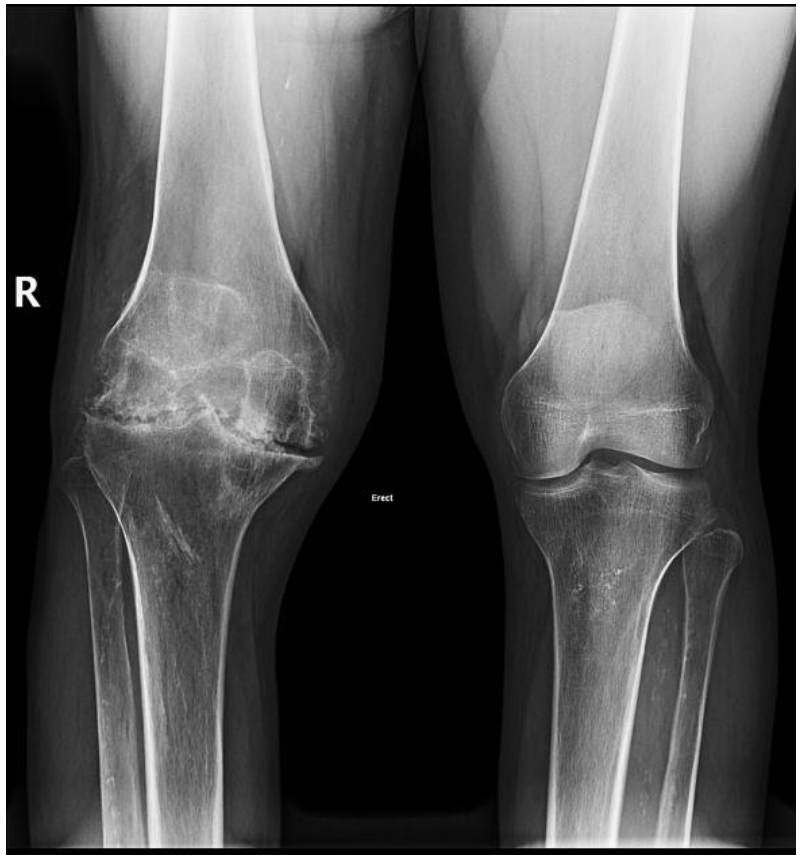
- Definition – a hereditary blood clotting disorder caused by mutations in factor VIII (antihemophilic factor, Xq28)
- Pattern – gonosomal (X-) recessive
- Affected gender – males
- Epidemiology – 1 in 5,000 males
- Mechanism
  - Unable to finish extrinsic pathway of coagulation
  - Failure to execute amplification phase

Haemophilia severity regarding FVIII concentration decrease

Severity	Factor level	Symptoms	Spontaneous bleeding	Managed at home?
Normal	0.5-1.5 IU/ml (50-150 %)	None	No	N/A
Mild	0.05-0.40 IU/ml (5-40 %)	Severe bleeding due to surgery or injury	No (rare)	Yes
Moderate	0.01-0.05 IU/ml (1-5 %)	Prolonged bleeding even at minor trauma/surgery	Occasional	Yes
Severe	<0.01 IU/ml (<1 %)	Spontaneous bleeding to muscles and joints	Yes	No







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https://www.researchgate.net/publication/221905236/figure/fig1/AS:281201312059421@1444055025924/Knee-joint-aspiration-This-technique-is-indicated-in-acute-and-profuse-haemarthroses.png
https://prod-images-static.radiopaedia.org/images/15199452/a554a4d2018c76bab7bc341e914cd4_big_gallery.JPG

Dental considerations

- If a neural block is necessary -> only after reaching of sufficient FVIII levels
  - Lingual infiltration requires same rules
- Intraligamental/interosseous techniques preferred compared to mandibular block
- Lower molar teeth -> articain (buccal infiltration)

- Risk of retromolar or pterygoid haematoma
  - Muscular bleeding
  - Airway obstruction

Acquired haemophilia A after Covid-19 mRNA vaccination?

- Symptoms developing 2 week after vaccination
- Age - >65 years (45-years-old woman reported)
- Parameters
  - Prolonged aPTT (up to 75 sec.)
  - FVIII activity – cca. 0.9–7 %
  - Sometimes FVIII inhibitor present (up to 12.8 BU/mL)
- Hypothesis – mRNA vaccine (or booster) may induce autoimmune response in predisposed people
- Occurrence – very rare

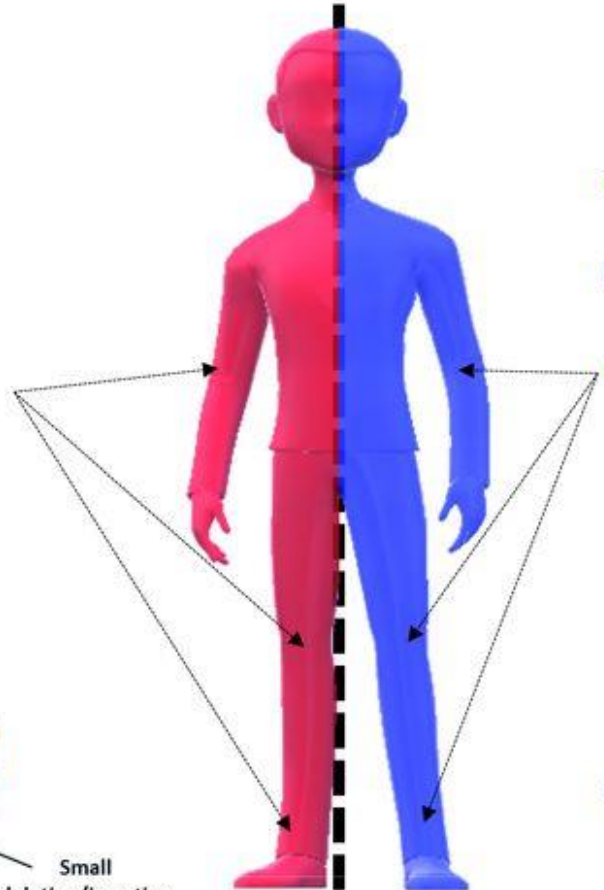
BU/mL – Bethesda units per millilitre – for measurement of blood clotting factors inhibitors

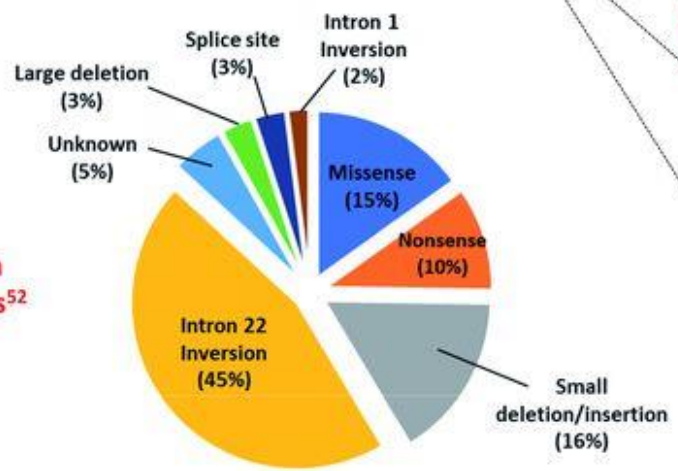
Hemophilia A

Prevalence: 1:5,000 males

Mode of inheritance: X-linked recessive

Clinical symptoms: Joint bleeding, muscle hematoma, soft tissue bleeding





F8 gene defects reported in severe Hemophilia A patients[52]

Characteristics of missing clotting factor (FVIII):

Function: Co-factor

Molecular Weight: 280 kDa[53]

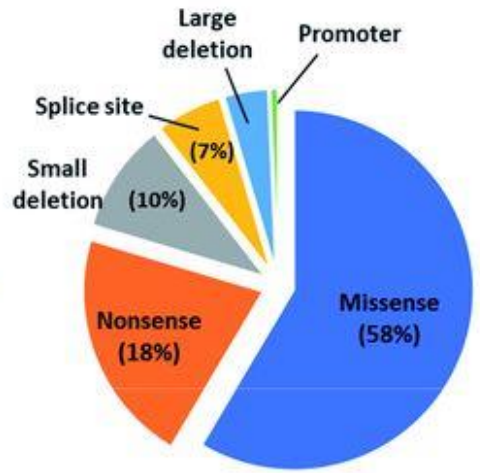
Normal concentration in plasma: 0.1-0.25 µg/mL

Hemophilia B

Prevalence 1:30,000 males

Mode of inheritance: X-linked recessive

Clinical symptoms: Joint bleeding, muscle hematoma, soft tissue bleeding



F9 gene defects reported in severe Hemophilia B patients[7]

Characteristics of missing clotting factor (FIX):

Function: Enzyme

Molecular Weight: 55 kDa[54]

Normal concentration in plasma: 3-5 µg/mL

https://haematologica.org/article/download/9037/64504/65112

Haemophilia B (Christmas disease)

- Cause – factor IX mutation (Xq27.1-27.2)
- Pattern – gonosomal (X-) recessive)
- Affected gender – males
- Epidemiology – 1 in 30,000 males
- Mechanism and symptoms – similar as haemophilia A

Members of the Royal Family with Hemophilia and Carriers of Hemophilia

Chart does not include unaffected family members

With Hemophilia

Carriers of Hemophilia

Queen Victoria
1819–1901, Age 81

Princess Alice, Grand Duchess
1843–1878, Age 35

Prince Leopold, Duke of Albany
1853 – 1884, Age 31

Princess Beatrice of Battenberg
1857–1944, Age 87

Princess Irene of
Hesse and by Rhine
1866–1953
Age 87

Prince Friedrich
of Hesse & by Rhine
1870–1873
Age 2½

Princess
Alexandra
1872–1918
Age 46

Princess Alice,
Countess of Athlone
1883–1981
Age 97

Princess Victoria
Eugenia of
Battenberg
1887–1969, Age 81

Prince Leopold
Mountbatten
1889–1922
Age 32

Prince Maurice
of Battenberg
1891–1914
Age 23

Prince Waldemar
of Prussia
1889–1945
Age 56

Prince Heinrich
of Prussia
1900–1904
Age 4

Grand Duchess
Maria
1899–1918
Age 19

Tsarevich
Nikolaevich Alexei
1904–1918
Age 13

Prince Rupert
of Teck
1907–1928
Age 20

Alfonso, Prince
of Asturias
1907–1938
Age 31

Infante Gonzalo
of Spain
1914–1934
Age 19

https://images.squarespace-cdn.com/content/v1/65c3bc3c5f3c855311eba919/1707436548225-HNRX9OFMOK63SNS8J6GT/Royal+Family.png

Haemophilia C (Rosenthal syndrome)

- Cause – factor XI deficiency (4q35, near prekallikrein)
- Pattern – autosomal recessive (partially)
  - Even heterozygotes may show bleeding manifestations
- Gender affected - both
- Epidemiology – 1 in 100,000 (2024), small communities predominantly
  - E.g. Ashkenazi Jews
- Mechanism – failure to sustain fibrin formation and prevention of fibrinolysis
- Symptoms – abnormal bleeding patterns
  - Oral bleeding, nosebleeds, haematuria, tonsils bleeding, postpartum bleeding
  - No bleeding in joints

Haemophilia summary

Severity	FVIII or FIX levels	Percentage of haemophilia A	Percentage of haemophilia B
Mild	5-40 %	43-70 %	50 %
Moderate	1-5 %	15-26 %	30 %
Severe	<1 %	15-31 %	Cca 20%

Note – heterogenity of FVIII mutation results in total not being 100 %

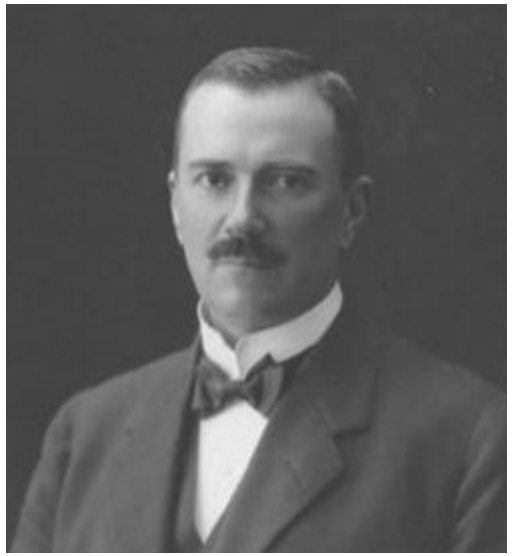
Parahaemophilia (Owren disease) is caused by factor V mutation (autosomal recessive, mild to fatal symptoms)

Feature	Hemophilia A	Hemophilia B	Hemophilia C
Deficient Factor	Factor VIII (FVIII)	Factor IX (FIX)	Factor XI (FXI)
Genetic Cause	Mutation in the F8 gene on X chromosome	Mutation in the F9 gene on X chromosome	Mutation in the F11 gene on chromosome 4
Inheritance Pattern	X-linked recessive	X-linked recessive	Autosomal recessive
Prevalence	Most common (80–85% of cases)	Less common (10–15% of cases)	Rare, mostly found in Ashkenazi Jewish populations
Severity	Can be mild, moderate, or severe	Can be mild, moderate, or severe	Usually mild to moderate
Clinical Manifestations	Spontaneous joint and muscle bleeding, prolonged bleeding after injury or surgery	Similar to Hemophilia A but may have milder symptoms	Post-surgical or trauma-related bleeding, not spontaneous bleeding
Prognosis & Management	FVIII replacement therapy, gene therapy in development	FIX replacement therapy, gene therapy in development	FXI replacement therapy, antifibrinolytics for mild cases

https://www.researchgate.net/publication/391222148/figure/tbl1/AS:11431281447927554@1747773115204/Comparison-of-hemophilia-A-B-and-C-in-terms-of-deficient-factor-genetic-cause.png

Von Willebrand disease

- Definition – a hereditary blood clotting disorder due to deficiency of quality or quantity of von Willebrand factor
  - necessary for platelets adhesion, binding to other proteins (especially FVIII)
- Epidemiology – cca. 1 % of population worldwide (most common coagulopathy)
- Pattern – autosomal dominant/recessive
- Gender – both



https://upload.wikimedia.org/wikipedia/en/thumb/e/e8/Eavonwillebrand.png/250px-Eavonwillebrand.png Dr. Erik Adolf von Willebrand (FIN, 1870 – 1949)

Type of von Willebrand disease

Type	Mechanism	Inherited	vWF activity	RIPA	Multimer quantity
1	↓vWF quantity	AD	↓	OK/↓	Similar decrease among multimer types
1C*					
2A	↓to form large multimers	AD/ar	↓	↓ (in high ristocetin)	Decreased large multimers
2B	↑binding to GP1B-receptor	AD	↓	↑	Decreased large multimers
2M	↓binding to GP1B-receptor	AD/Ar	↓	↓ (in high ristocetin)	Similar decrease among multimer types
2N**	↓binding to FVIII	ar	Normal	OK	Normal
3	Absent vWF	ar	None or ↓↓↓	None or ↓↓↓	Usually undetectable

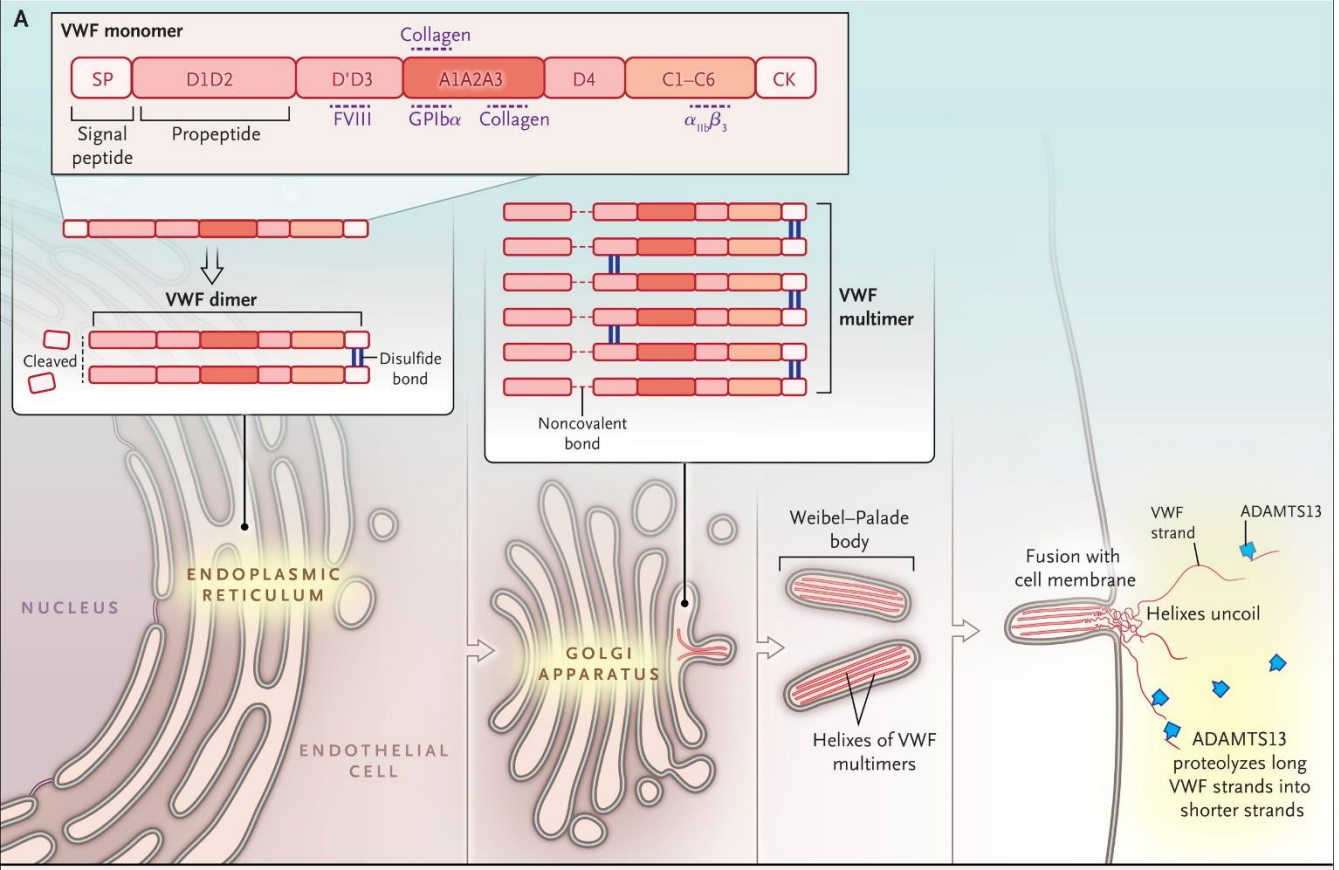
* - C means increased cleavage of vWF
** - N stands for „Normandy", FVIII levels are low due to insufficient binding to vWF (5-15 %), resembling haemophilia A
RIPA – ristocetin-induced platelet aggregation (ristocetin is an antibiotic agent used also for platelets assay)

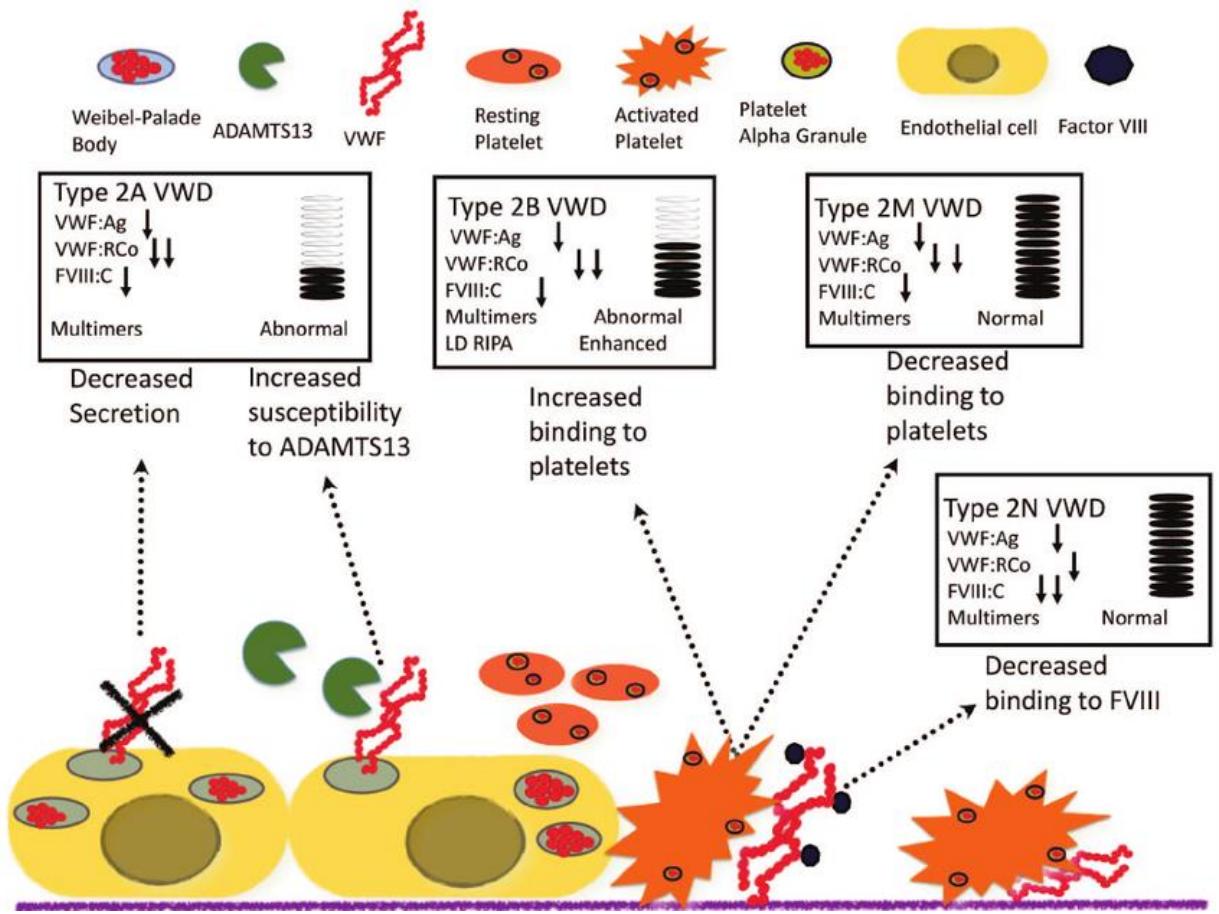
Von Willebrand disease

- Pathomechanism
  - Deficiency affects blood flow and shear stress in capillaries
  - Improper binding leads to decreased platelets adhesion -> bleeding
  - Affecting organs with small capillaries -> e.g. skin, GIT, uterus
  - Influence of AB0 system
    - 0 – decreased levels of vWF (prone to manifestation); AB – elevated vWF (often silent)
- Manifestation
  - Bruising, nosebleeds, bleeding gums
  - Hypermenorrhoea or blood loss during childbirth
  - Internal bleeding or joints bleeding (Type 3)

Dental considerations

- Oral manifestations
  - Severe vWF deficiency -> spontaneous gingival bleeding, ecchymoses, epistaxis
  - Oral contraceptives -> gingival enlargement possible -> worse symptoms
  - Hemosiderin depositions on teeth – brown discoloration
  - Most common bleeding locations - labial frenum (60 %), tongue (23 %), buccal mucosa (17 %) and gingiva and palate (0.5 %)
- Recommendations
  - Use factor concentrate + local suturing techniques (oxidised cellulose, Surgicel, fibrin glue)
  - NSAIDs use discussed with haematologist!





Physiological function of vWF (left), examples subtypes of vWF disease (above)

https://www.nejm.org/cms/asset/e36c78c2-ec77-4aaf-8690-a600703b1c2b/nejmra1601561_f1.jpg
https://www.researchgate.net/publication/233902013/figure/fig3/AS:300086740439042@1448557662532/Mechanism-of-disease-for-qualitative-variants-type-2-VWD-and-the-effect-on-diagnostic.png

Other important subtypes of vWF disease

- Platelet-type (pseudo-vWF disease)
  - AD platelets defects -> GB1P enhanced binding to vWF -> large platelet aggregates and vWF multimers -> removal from blood -> low vWF
- Acquired
  - Enhanced cleansing (shear stress), interference with platelets binding, adsorption to myeloma cells or platelets, antibodies
  - Heyde‘s syndrome -> enhanced GIT bleeding in aortic valve stenosis
    - Bleeding improves after correction, relapse possible (poor prosthetic valve)
  - Left ventricular assist device (heart pump)

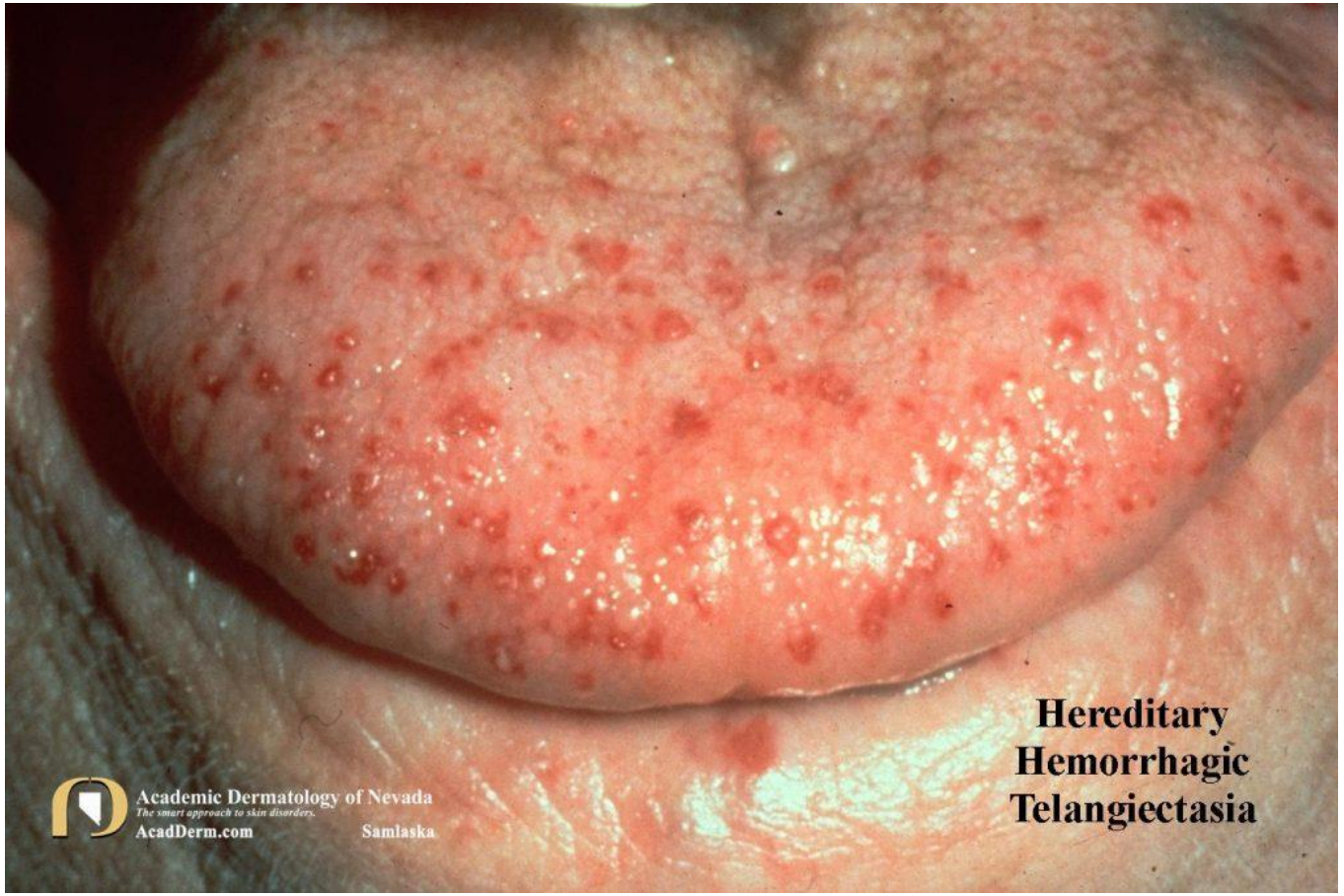
Vasculopathies

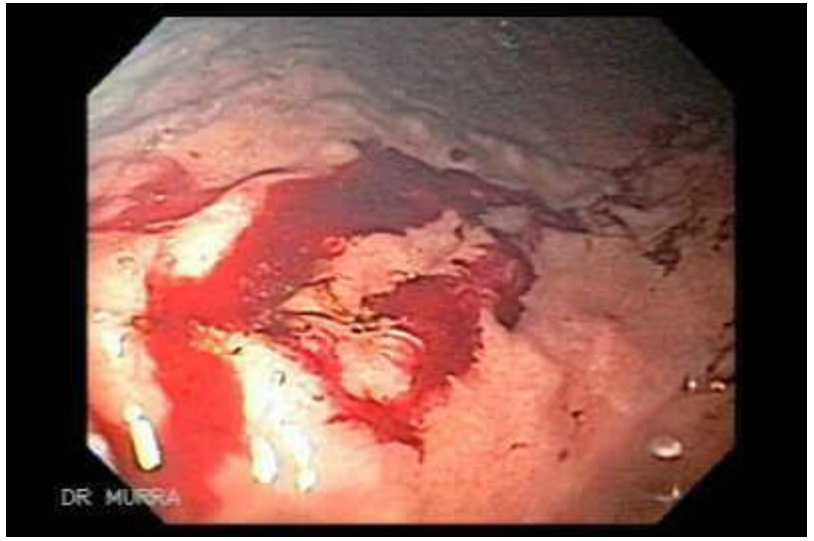
Vasculitis and vasculopathies

- Definition – an inflammatory process (autoimmune frequently) targeting endothelial layer of blood vessels
- May attack both arteries and veins
- May attack large, medium and small-calibre vessels
- May or may not be associated with disorders of coagulation
  - Bleeding disorders – e.g. m. Rendu-Osler(-Weber)
  - Thrombophilia states – (deep) venous thrombosis

Rendu-Osler-Weber syndrome (hereditary haemorrhagic telangiectasia)

- Definition – a rare hereditary vasculitis associated with vessel malformations and bleeding diathesis
- Pattern – autosomal dominant (both genders)
  - Mutation in genes ENG (9q34.1), ACVRL1 (12q11-14), MADH4 (18q21.1, unknown in ch. 5q31, 7p14
- Prevalence – 1:5,000-1:10,000 worldwide (2024)
- Mechanism and manifestations
  - Arteriovenous malformations -> telangiectasia, pulmonary hypertension
  - Fragile vessels formation -> enhanced bleeding -> nosebleeds, Git haemorrhage, stroke, haemoptysis, etc.
  - Large intestines polyps (MADH4), thrombosis also possible





https://acadderm.com/wp-content/uploads/2019/11/HHT3Samlaska-1024x683.jpg
https://www.gastrointestinalatlas.com/imagenes/Telangiectasia7.jpg

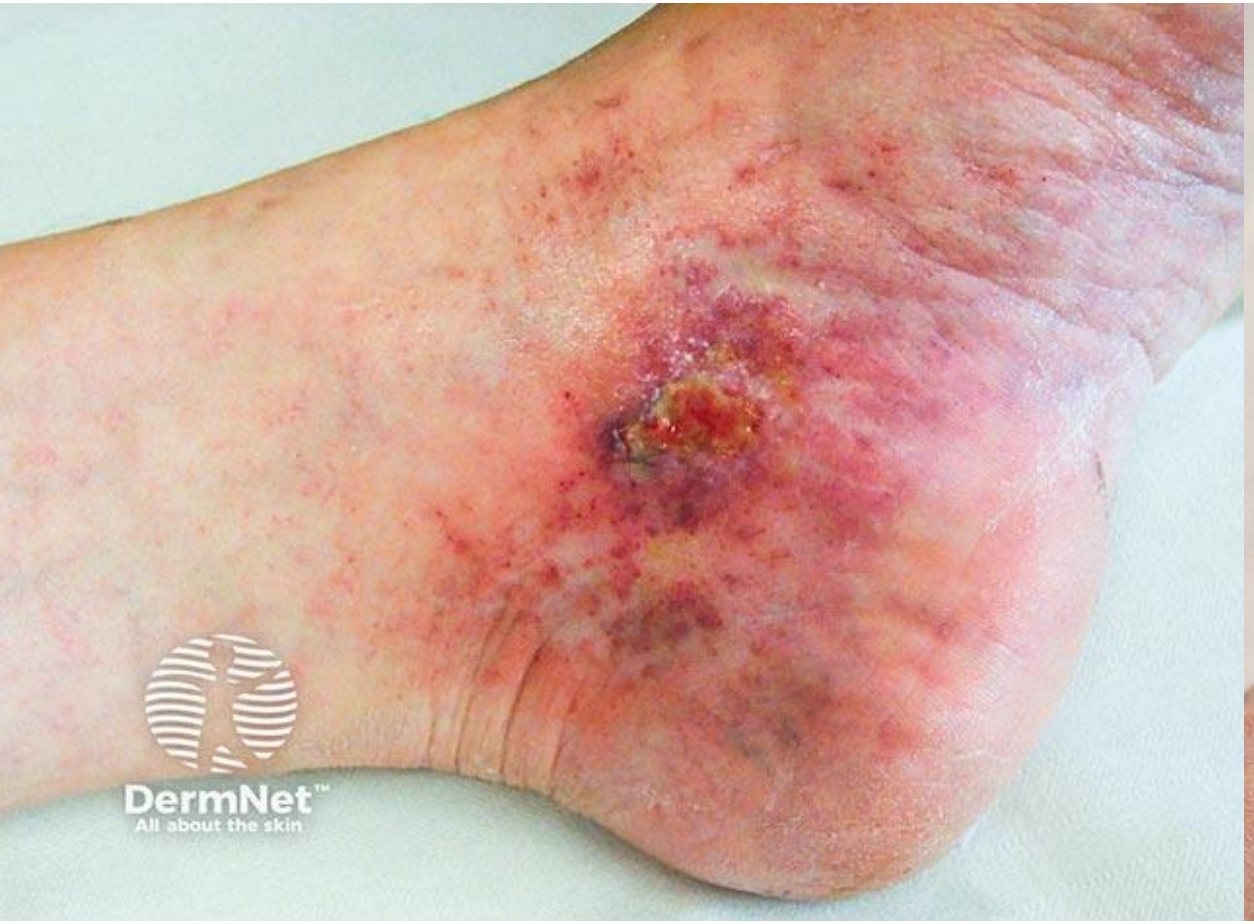
Livedoid vasculopathy

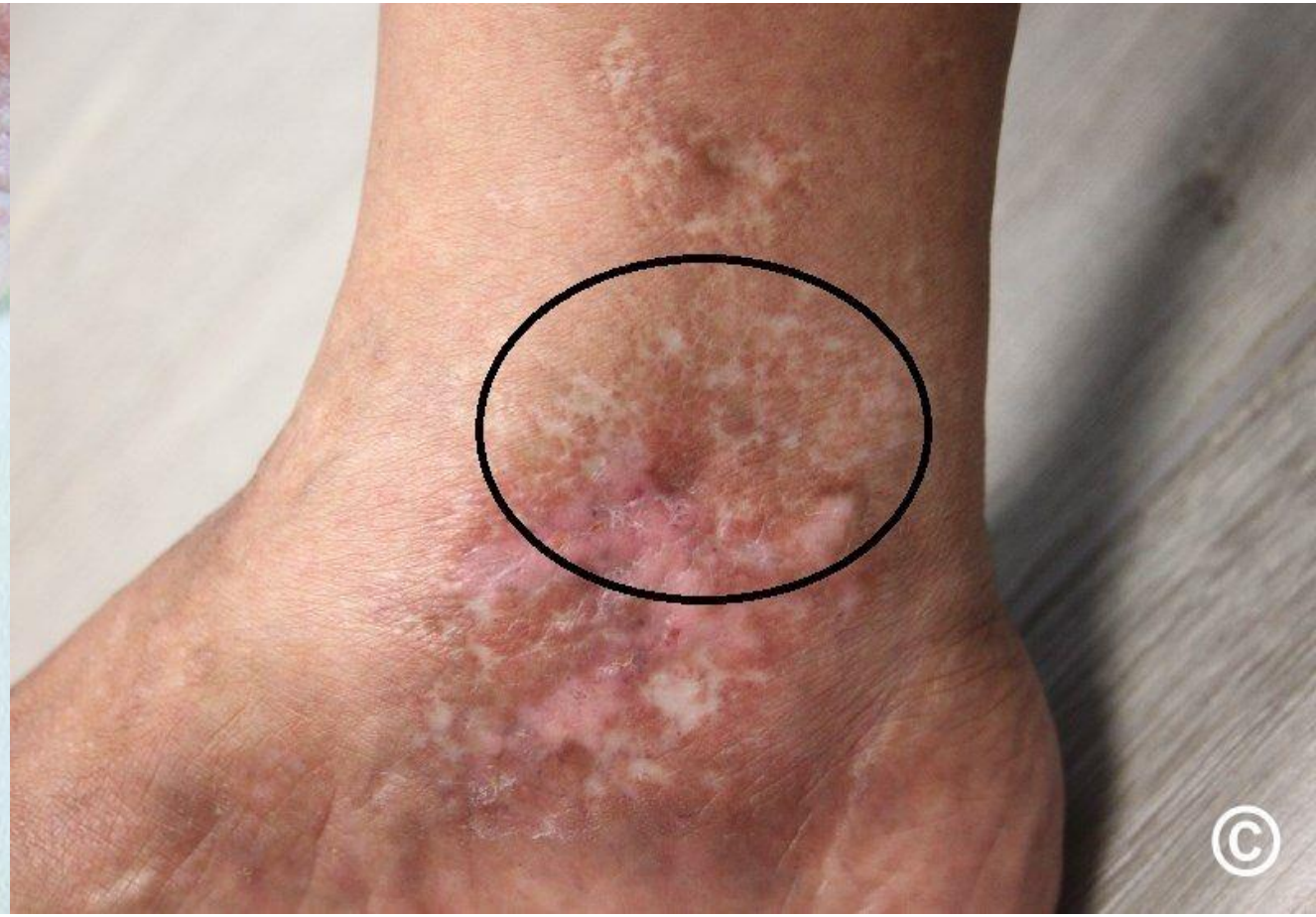
- Definition – an uncommon thrombotic dermal vasculopathy with excruciating, recurrent ulcers on the lower limbs
- Cause and pattern – unknown
- Prevalence – 1:100,000 worldwide (2022) -> M:W = 1:3
- Causes
  - Genetics -> polymorphisms in FV, PAI-1, prothrombin, MTHFR
  - Autoimmune diseases -> rheumatoid arthritis SLE, scleroderma, polyarthritis nodosa, Sjögren syndrome, connective tissues disease
  - Antiphospholipid antibodies increase risk

MTHFR – methylenetetrahydrofolate reductase

Livedoid vasculopathy

- Mechanism
  - Endothelial dysfunction, reduced plasminogen activity, platelets abnormalities, fibrin formation alteration -> thrombotic effect
  - Fibrin deposition and thrombi -> tissue hypoxia -> necrosis
  - Insufficient wound healing -> vicious circle -> ulcerations
- Manifestations
  - Livedo racemosa
  - Ulcerations -> healed with porcelain-white scars
- Currently, only symptomatic treatment is available (pain reduction, etc.)





https://dermnetnz.org/assets/collection/Atrophie-blanche/atrophie-blanche-0007.jpg
https://www.pcds.org.uk/imager/gallery/clinical/livedo-reticularis/11126/Liv_ret11_fee391183f15cb4d62773032fe0be92d.jpg

Deep vein thrombosis (phlebothrombosis)

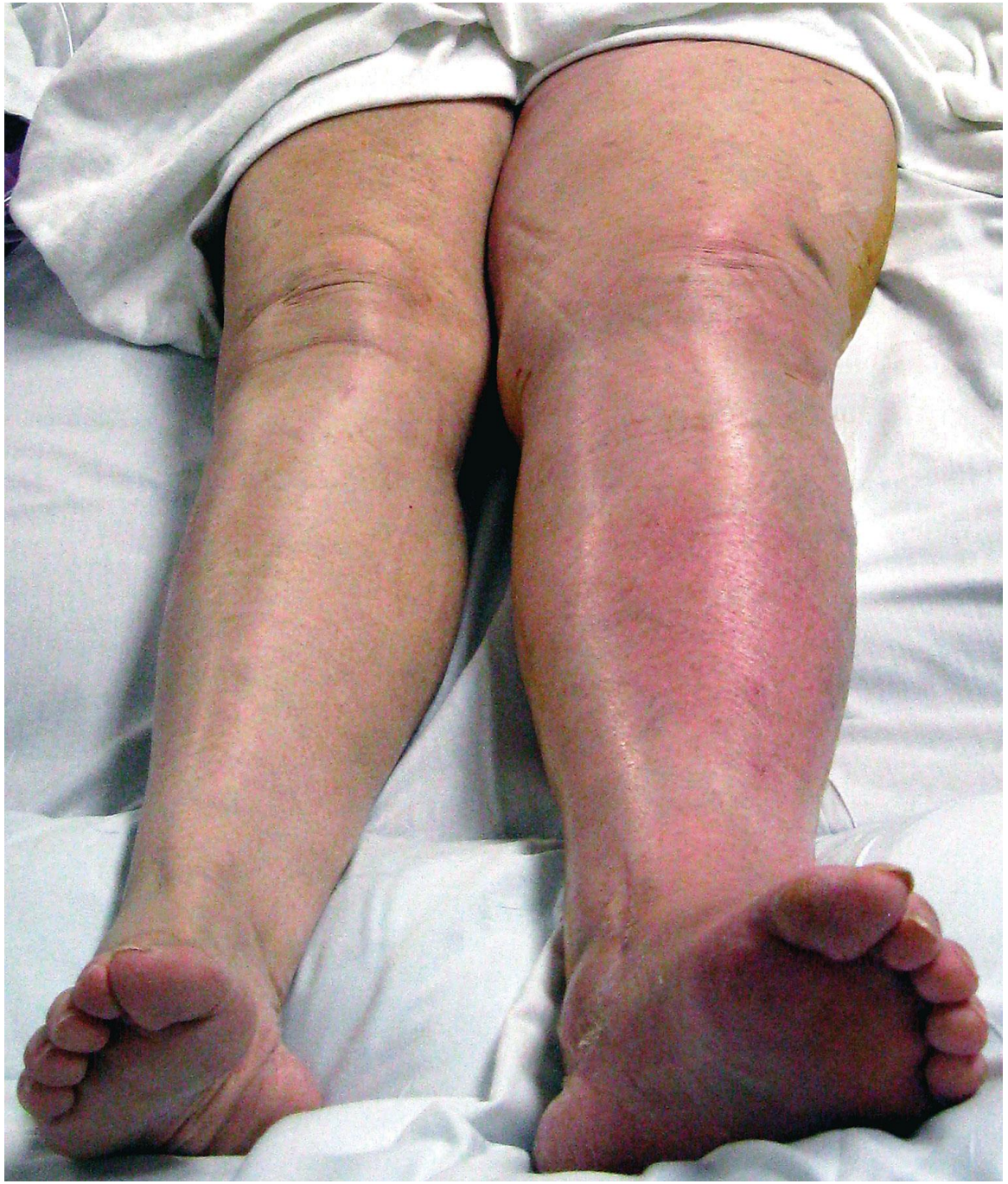
- Definition – a blood clot formation in deep vein system often resulting into potential complications e.g. pulmonary embolism
- Prevalence – 1.5:1,000 (2023)
- Risk factors
  - Non-modifiable – age (old), family history, female gender (?)
  - Modifiable – pregnancy, cancer, oral contraceptives, obesity, inflammation, autoimmune diseases, immobility, prolonged surgeries (!), etc.
- Classification
  - Iliofemoral DVT
  - Proximal DVT -> above knee region
  - Distal DVT -> below

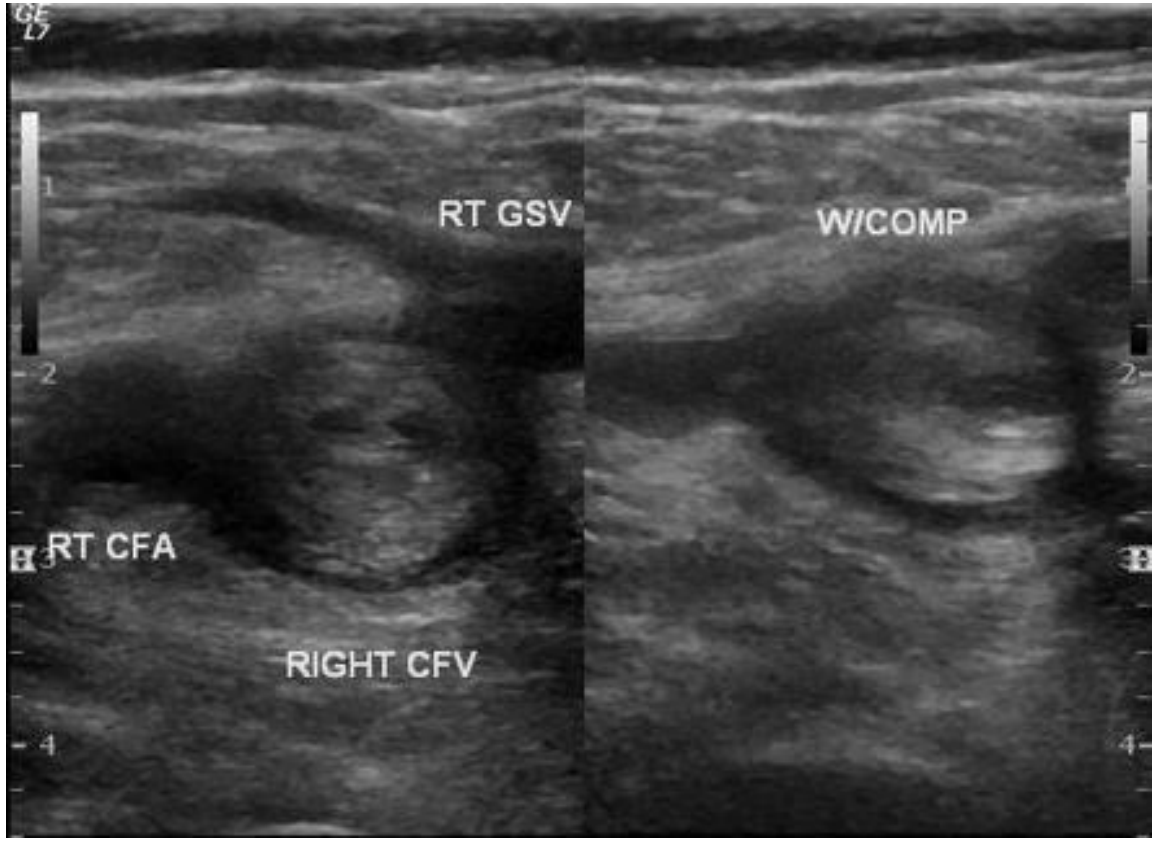
Deep vein thrombosis (phlebothrombosis)

- Mechanism -> disruption of Virchow triad
  - Endothelial dysfunction as the main trigger -> vein wall inflammation
  - Interactions endothelium-leucocytes -> leucocytes start to facilitate clotting
  - Neutrophils activated -> NETs formation
  - Monocytes stimulated to release tissue factor -> TF-FVIIa -> extrinsic pathway of coagulation activated
  - Malignancies can stimulate FXa directly
  - Hypoxic cascades triggered -> monocytes adhesion -> growth of thrombus
- D-dimers elevated

Deep vein thrombosis (phlebothrombosis)

- Manifestations
  - Pain, swelling, redness and enlarged veins
  - Positive Hommans sign
  - Some might be asymptomatic
  - Pulmonary embolism (33 % of cases) -> dyspnoea, right heart failure
- Prevention
  - „vascular exercise“ -> toe-to-heel switch
  - Compressive stockings



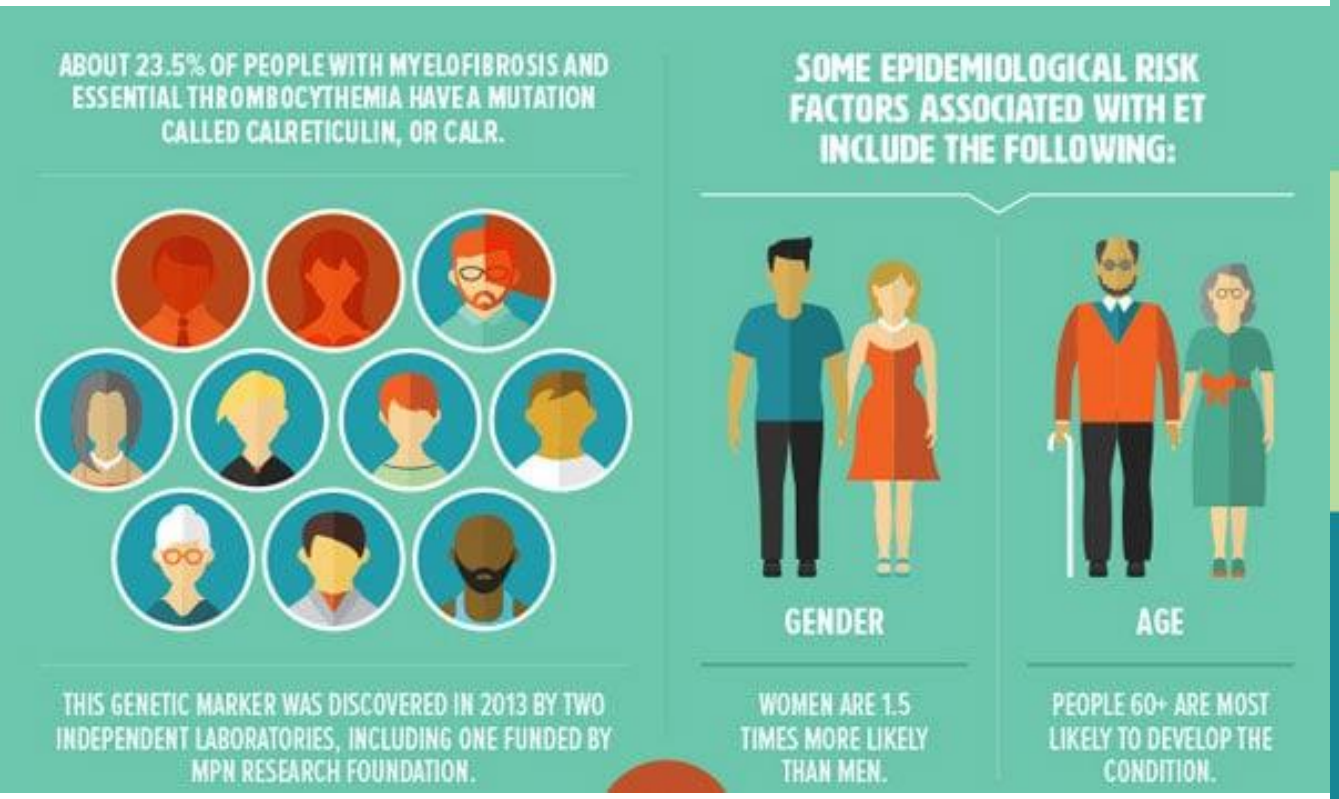


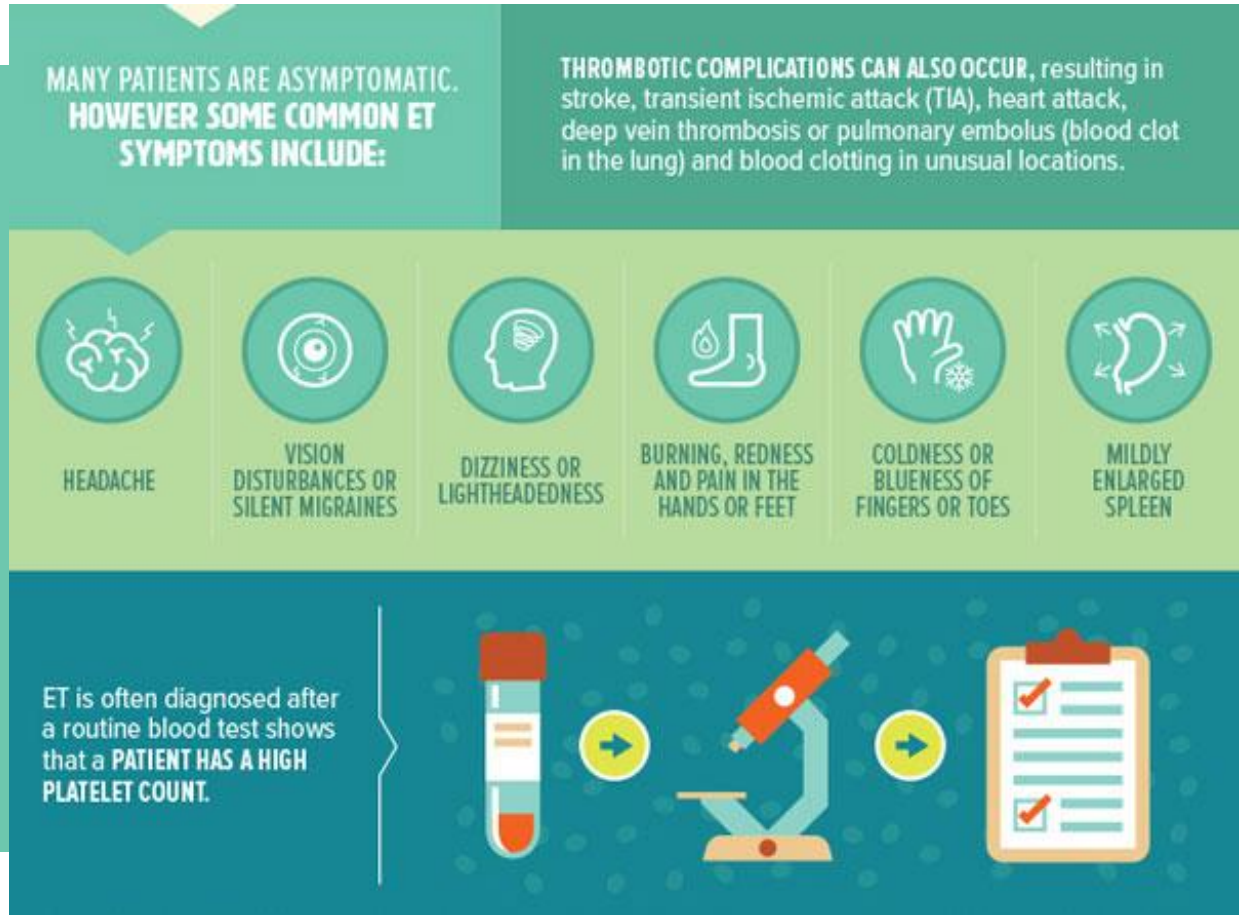
https://www.venousforum.org/wp-content/uploads/2024/03/Fig-23-1.jpg
https://prod-images-static.radiopaedia.org/images/3463851/09947177efd17d272bd4ba5ac048e9_gallery.jpg

Elvated platelets counts

Thrombocytosis (thrombocythemia)

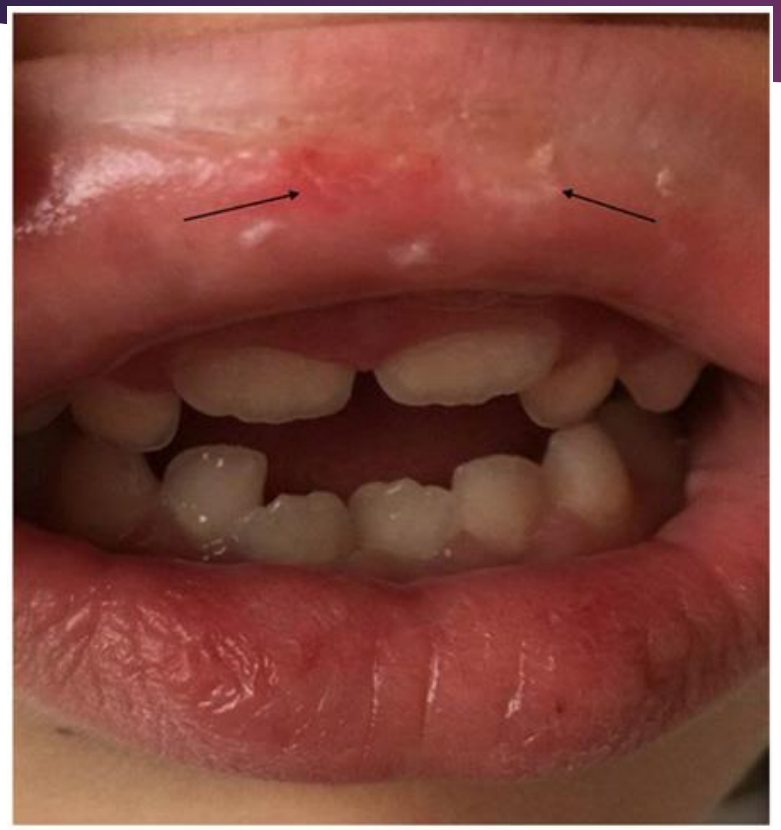
- Platelets count elevated in peripheral blood >750 000 cells/μl (reference range >420 000 cells/μl) with or without platelets function affected
- Causes
  - Myeloproliferation states – primary (essential), CML, polycythaemia vera, primary myelofibrosis
  - Reactive – 88–97 % of adult thrombocythemia (almost 100 % in children)
    - Acute infection, chronic infection, tissue damage, malignancies; SARS, post-surgical states, drugs, iron deficiency, „rebound“ phenomenon after bone marrow suppression, physical activity
    - Asymptomatic mostly
  - False positive – platelets-like elements presence – cryoglobulin crystals, leukemic cells debris, bacteria, red blood cells microvesicles
- Erythromelalgia – burning sensation in red coloured limb -> aspirin and/or cold relieve the sensation
- Thrombophilia does not automatically mean thrombocythemia!

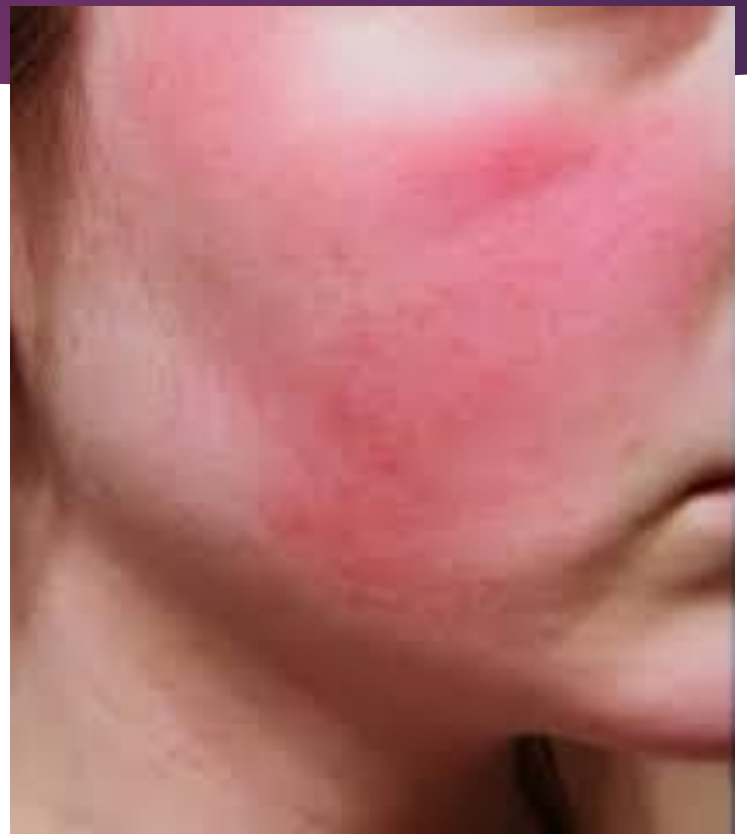


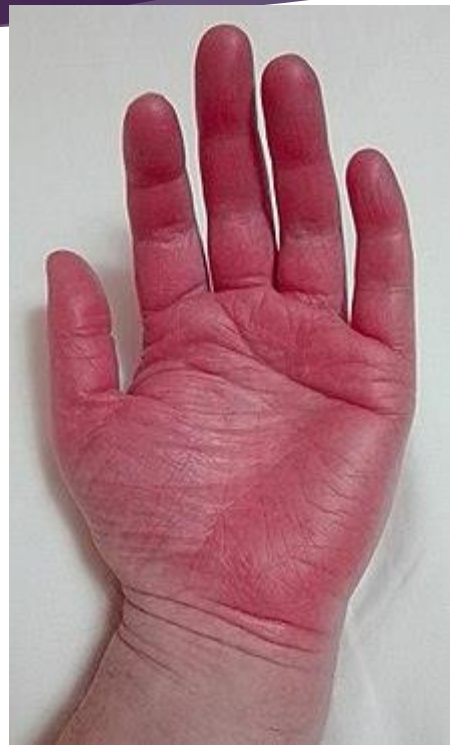


https://hohmanrehab.com/wp-content/uploads/2020/10/Essential-Trombocythemia-Statistics.jpg
https://images.ctfassets.net/tytuahdkbx9m/patientpower_ArticlePage_asset_45741d58b054f6f62f31e6e9bc5278349/47e05bd75d570184832ed8706fcfc243/patientpower_ArticlePage_asset_45741d58b054f6f62f31e6e9bc5278349

Platelets count and function disorders in oral cavity manifestation – erythromelalgia (hand as a comparison)







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https://encrypted-tbn0.gstatic.com/images?q=tbn:ANd9GcTF5bHOwDD-JlNt4zel88s1NH2kwY4yP3EF2Q&s
https://upload.wikimedia.org/wikipedia/commons/thumb/7/72/Erythromelalgia_in_hands.jpg/220px-Erythromelalgia_in_hands.jpg

Increased coagulation

THROMBOPHILIA STATES

Thrombophilia states – inherited

- **Antithrombin III deficiency**
- **Factor V Leiden mutation**
- Prothrombin G20210A mutation
- Antithrombin deficiency
- **Protein C deficiency**
- **Protein S deficiency**
- Sticky platelets syndrome
  - AD mutation -> platelets overactivity to ADP or epinephrine
- Hyperhomocysteinemia (may be acquired – vitamin B9, B12 deficiency)

Antithrombin III deficiency

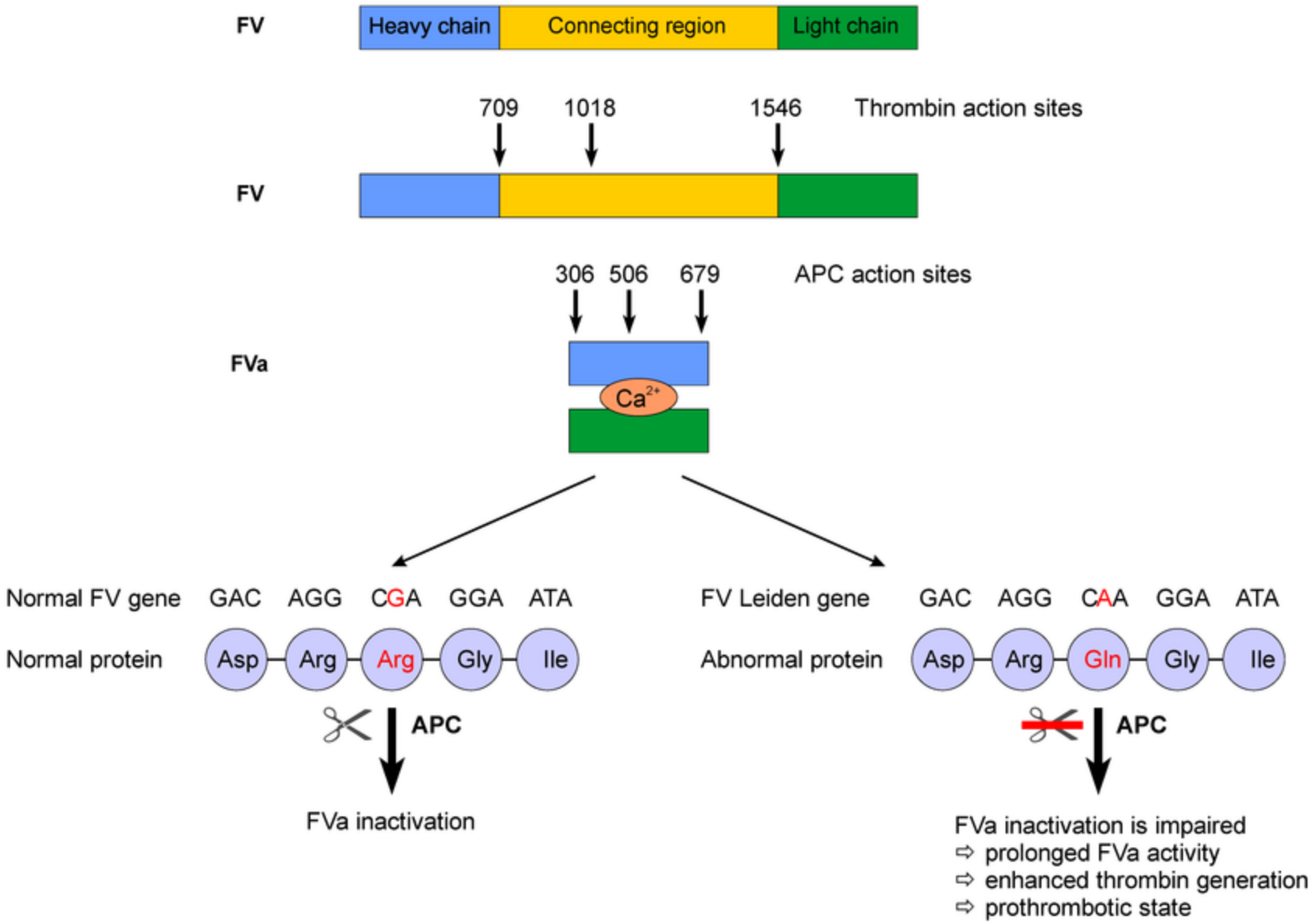
- Definition – a hypercoagulable state disorder with dysfunctional or deficient antithrombin III
- Prevalence – 1:500 (both genders)
- Pattern – autosomal dominant (only heterozygotes survive, homozygotes with HBS affected)
- Mechanism
  - SERPINC1 mutation -> reduced ATIII
  - Decreased quantity (type I) or quality (type II - heparin-binding site (HBS), the reactive site (RS) or result in pleiotropic effects (PE))
- Highest risk of thrombosis in inherited thrombophilia -> DVT/pulm. embolism
- Acquired - nephrotic syndrome, enteropathy, DIC, sepsis, burn, trauma, microangiopathy, and cardiopulmonary bypass surgery

Factor V Leiden

- Definition – the most common hypercoagulability state due to genetic mutation in gene for factor V
- Pattern – autosomal dominant (incomplete penetrance; rs6025 or F5 p.R506Q)
- Gender – both
- Mechanism
  - Mutated factor V is unable to bind to protein C -> hypercoagulability state
  - Heterozygotes might be unaffected (unless other factors present)
  - Increased risk for deep venous thrombosis

Factor V Leiden

- Manifestations
  - Deep venous thrombosis (DVT) or pulmonary embolism (PE) before 50 years of age
  - Recurring DVT or PE
  - DVT in unusual locations – e.g. brain, liver
  - Pregnancy or postpartum DVT/PE
  - Spontaneous unexplained abortions
  - Positive family history
- Danger – hormonal medications -> oral contraceptives (oestrogen based) or hormonal replacement therapy -> 35-times risk (to women without medication and FV Leiden mutation)



https://www.researchgate.net/publication/371561255/figure/fig1/AS:11431281420610889@1746259833708/Factor-V-Leiden-is-an-abnormal-protein-the-result-of-a-single-point-mutation-at-position.tif

Source: author‘s work

Protein C and protein S deficiency

- Definition – hypercoagulative states caused by a defective function or synthesis of protein C and/or protein S
- Causes
  - Genetic (overall)
    - Missense mutations (60–70 %), nonsense mutations (1-15 %), splice site mutations, large deletions, duplications, insertions, point mutations
- Epidemiology (2023)
  - Protein C – 1:200-1:500 (asymptomatic), 1:20,000 (DVT)
  - Protein S – unknown (3:10,000-13:10,000)

Protein C deficiency

- No clear racial or ethnical predispositions
- Genetic causes
  - PROC gene (2q14.3) -> cca. 160 mutations
    1. Type I - Low protein C antigen and activity
    2. Type II – Normal protein C antigen and low activity
  - Acquired
    - Inflammatory diseases, malignancies, chemotherapy, liver diseases, disseminated intravascular coagulopathy, vitamin K deficiency, vitamin K antagonists
- New-born babies have only 35 % levels of protein C -> normalisation within 6-12 months of age

Protein S deficiency

- Genetic (inherited)
  - Autosomal dominant -> mutations in PROS1 gene (3q11.1) – up to 200 mutations
    1. Type I (quantity) – low total protein S, low free protein S, low protein S activity
    2. Type II (quality) – normal total protein S, normal free protein S, low protein S activity
    3. Type III (quantity) – normal total protein S, low free protein S, low protein S activity
- Acquired
  - Liver disease, inflammation, nephrotic syndrome, DIC, chemotherapy, malignancy, pregnancy, oral contraceptives, hormone-replacement therapy, vitamin K deficiency and vitamin K antagonists
- New-borns – low protein S levels -> normalisation in 6-10 months of age

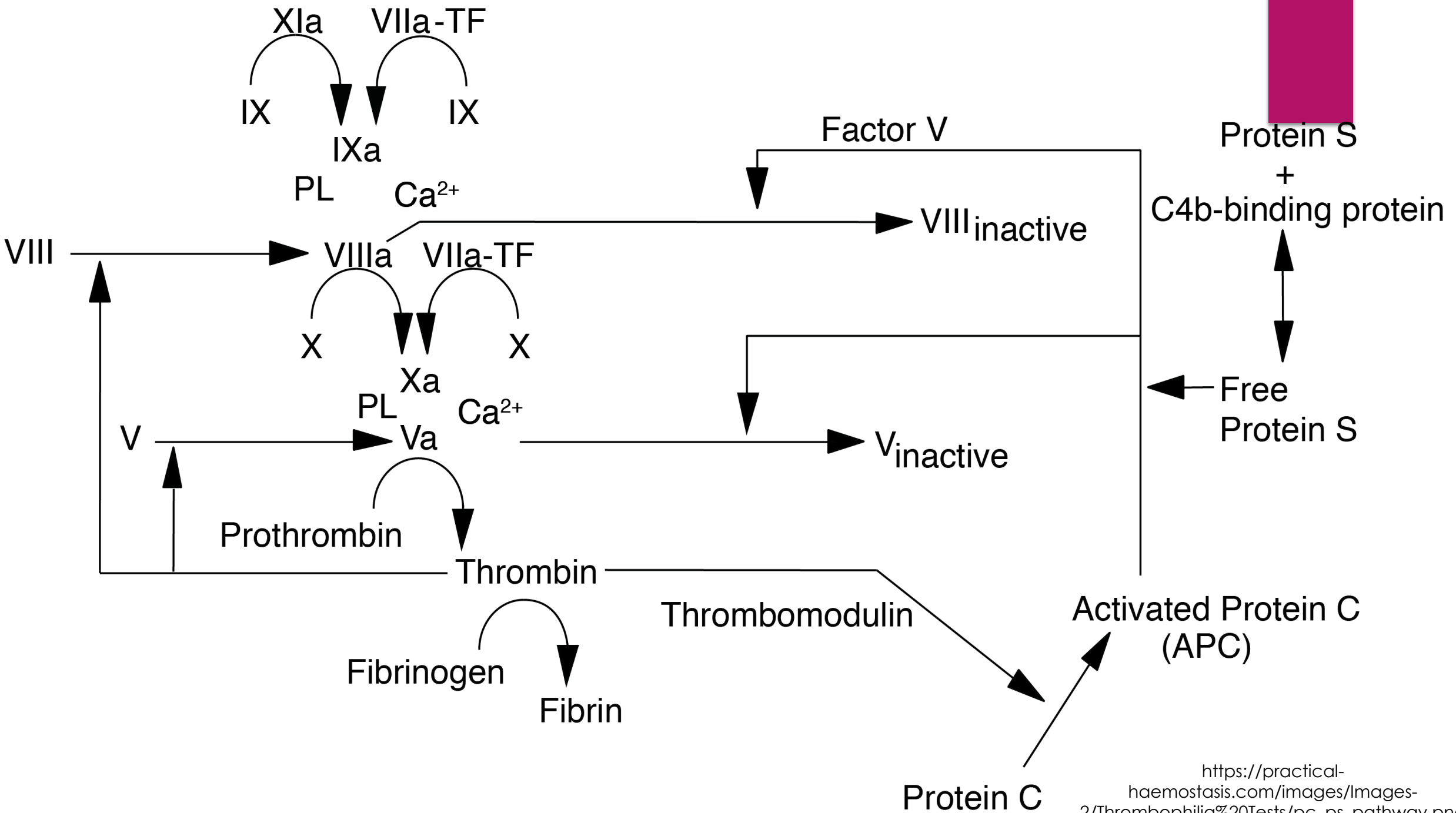
Mechanism of proteins S and C action

- Protein C and S -> produced in liver (S also in platelets, endothelial cells, osteoblasts, vascular smooth muscle cells)
- Mechanism
  - Thrombin-thrombomodulin complex -> protein C activation
    - Protein C + free protein S + phospholipids + Ca^{2+} -> FV and FVIIIa inactivation
    - Reduced thrombin generation -> anti-coagulant function
  - Protein S + C4-binding protein complex (60-70 % of protein S)
    - FVa cleavage (less effective as free protein S)
  - Protein S -> enhancing protein C in fibrinolysis
  - Protein S -> FX inactivation (tissue factor pathway inhibition)

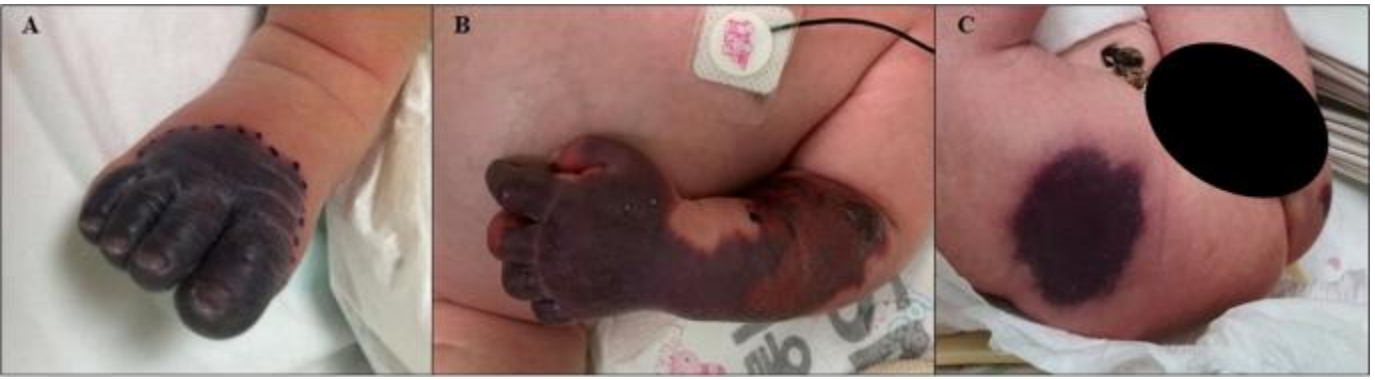
Pathomechanism of hypercoagulability in protein C and S

- Protein C and S deficiency -> hyperactivity of FV and FVIII -> excessive thrombin
- Factor V Leiden
  - G1691A mutation -> Arg->Gln -> prevention of deactivation by activated protein C and S

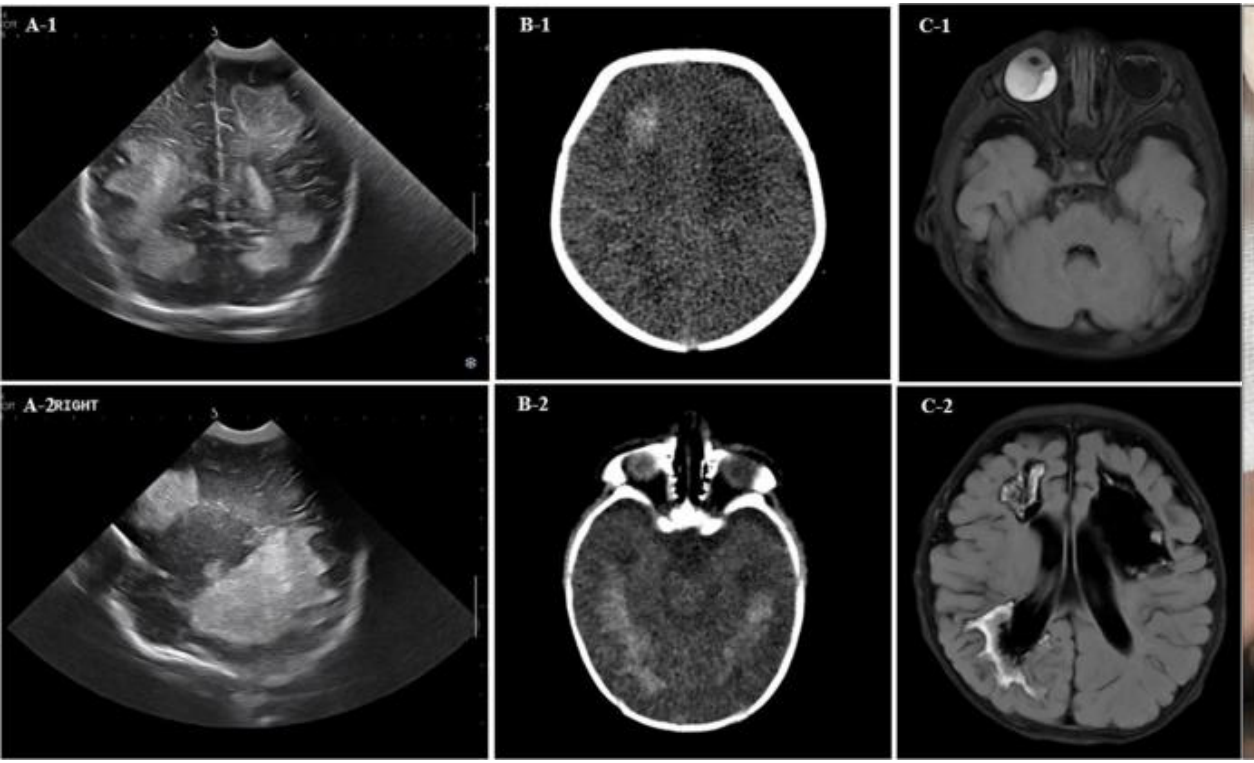
- Warfarin-induced skin necrosis is mostly due to protein C deficiency but rare cases report also protein S deficiency

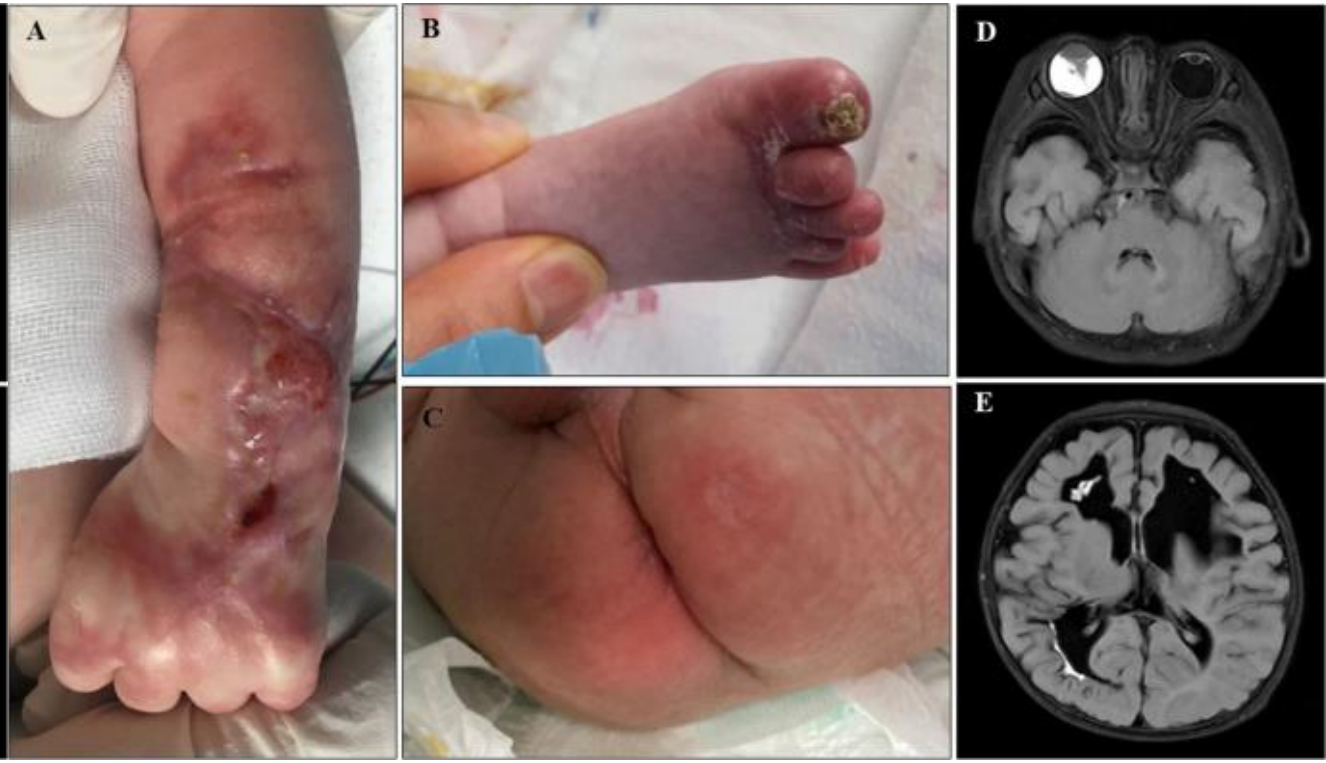


https://practical-haemostasis.com/images/Images-2/Thrombophilia%20Tests/pc_ps_pathway.png



Purpura fulminans after birth (protein C deficiency)





Lesions 6th day (some occurred in utero)

2 months of age – treated by protein C concentrate

https://bmcpediatr.biomedcentral.com/articles/10.1186/s12887-021-02923-6

Antiphospholipid syndrome (APS)

- Definition – an autoimmune hypercoagulable state by antiphospholipid antibodies (anti-PL)
- Prevalence – 50:100,000 women, 9,8:100,000 men (2022)
- Cause – unclear (possible genetic influence)
- Mechanism
  - Anticardiolipin-Ab, β2-glycoprotein 1, lupus anticoagulant -> antibodies in APS
    - Anti-ApoH -> binds to ApoH -> protein C activity inhibition
    - Antibodies against protein S and Annexin A5 (shielding negative surfaces -> coagulation prevention)

Antiphospholipid syndrome (APS)

- Manifestations
  - Decreased trophoblast activity -> miscarriage, intrauterine growth restriction, pre-term birth, preeclampsia, eclampsia
  - DVT -> pulmonary embolism
  - Organs may be affected -> kidney, heart, skin rash
  - Low platelets detected often
- Classification
  - Primary – no other disease present
  - Secondary – caused by another process
- CAPS (catastrophic APS/Asherson syndrome) – rapid organ failure due to thrombosis

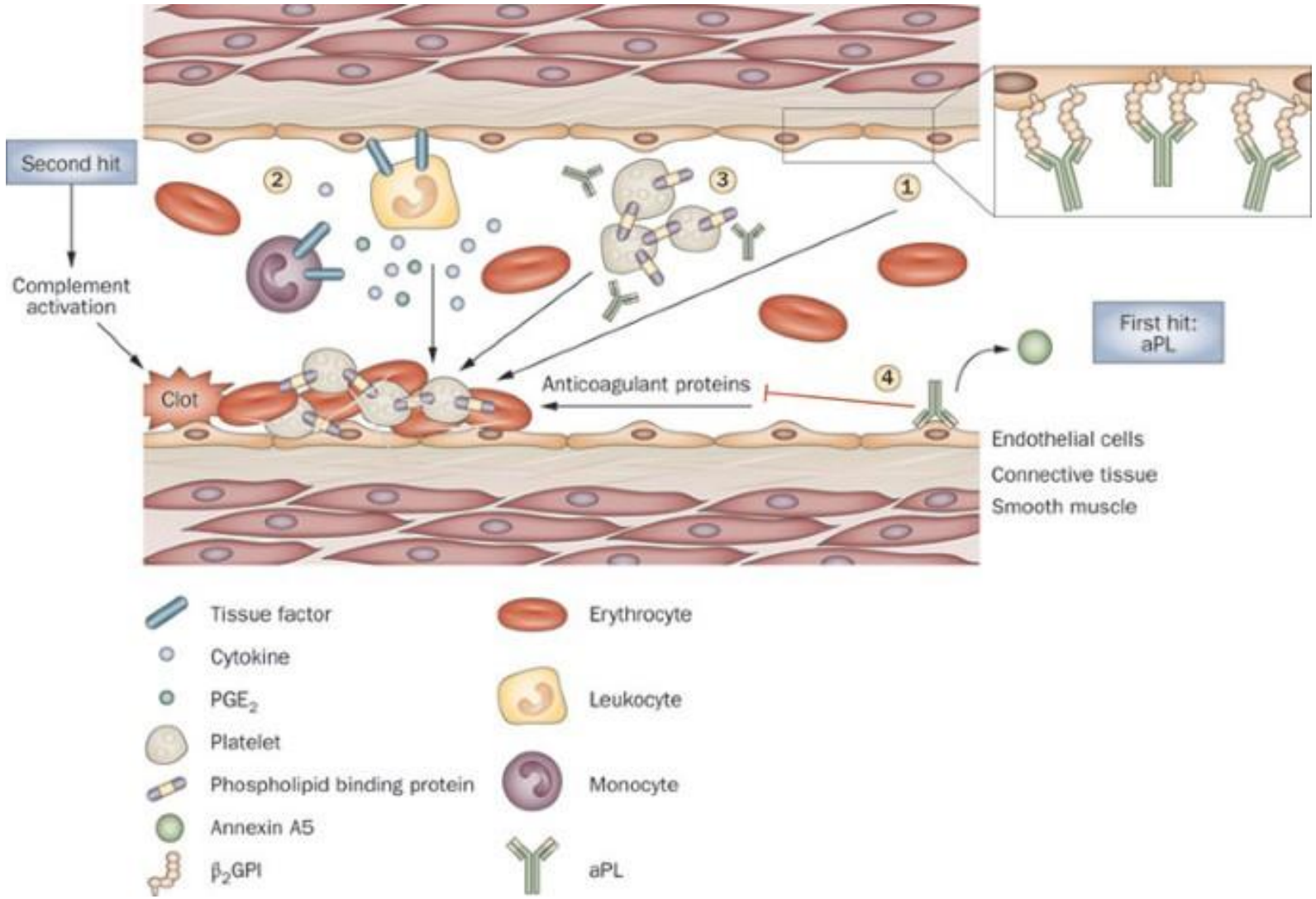


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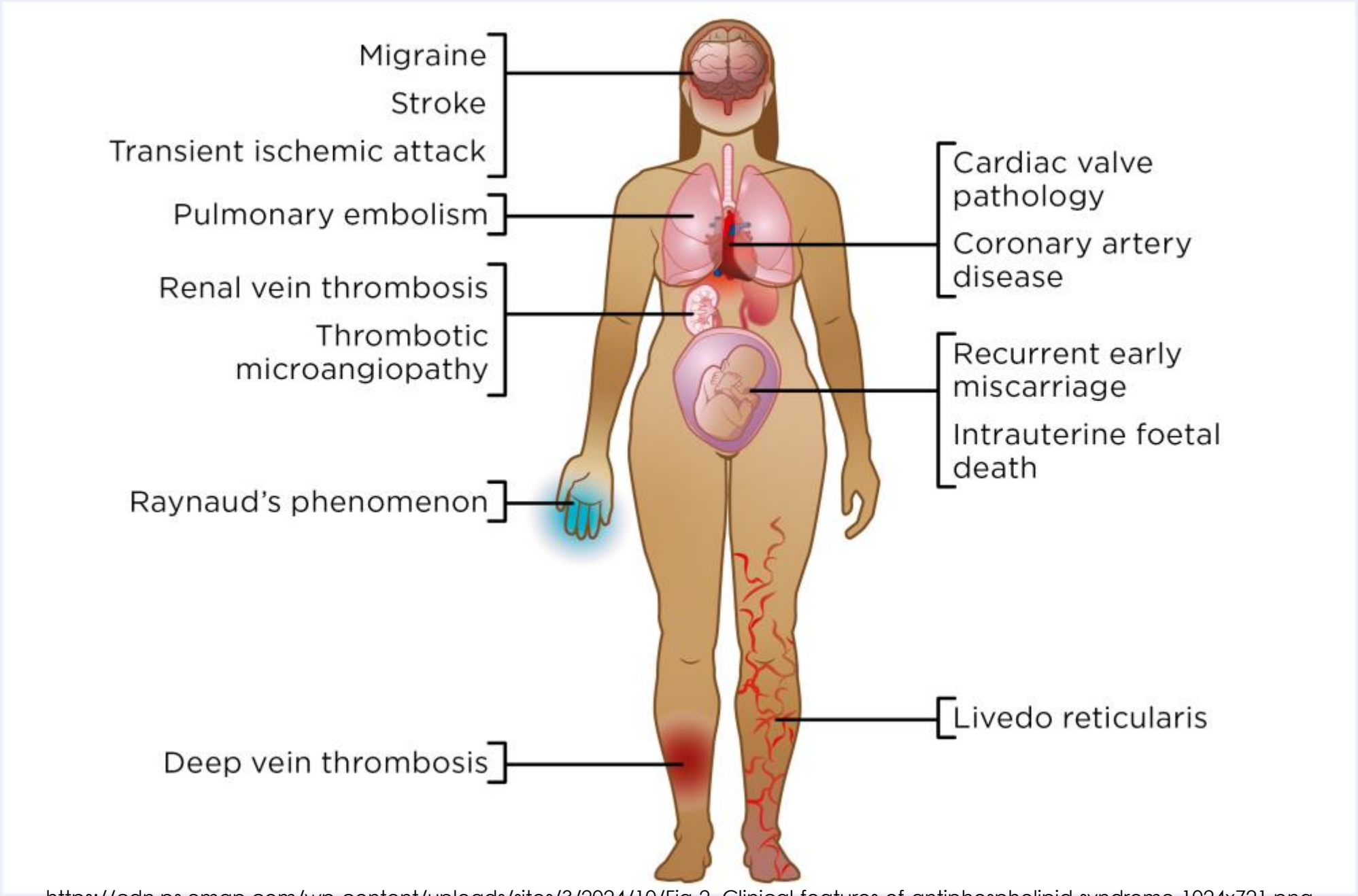
Fig 2. Clinical features of antiphospholipid syndrome



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Acquired thrombophilia states

- Malignancy
  - Tumour producing inflammatory cytokines -> possible SIRS
  - Interaction with platelets, monocytes, neutrophils and vascular cells -> tumour thrombus formation
  - Slowing down blood flow
  - Chemotherapy may worsen the effect
- Pregnancy
  - Elevated FVII, FVIII, FX and fibrinogen
  - Decreased protein S, increased resistance to activated protein C
  - Reduced fibrinolytic activity -> increased PAI-1 and PAI-2
  - Uterus may pressure on inferior vena cava -> DVT -> pulmonary embolism

Acquired thrombophilia states

- Surgery and trauma
  - Tissue trauma + inflammatory reaction + possible blood stasis
- Certain medications, such as oral contraceptives
  - FVII, FX and fibrinogen production elevated
  - Reduced antithrombin III and protein S, etc.
- Obesity
  - Chronic low-grade inflammation
  - Endothelial dysfunction
  - Reduced fibrinolytic activity
  - Enhanced secretion of coagulation factors

Acquired thrombophilia states

- Prolonged immobility
  - Venous stasis + endothelial injury + inflammation
- Certain infections
  - CMV
- Heparin-induced thrombocytopenia (HIT)
  - Antibodies against platelet factor 4 (PF4) and heparin
  - Most frequent in unfractioned heparin administration, LMW-heparin at lower risk

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