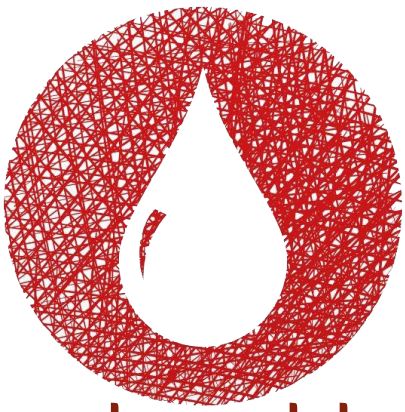
جامعة الملك سعود
King Saud University

MED437
KING SAUD UNIVERSITY



Approach to bleeding disorder

Objectives :

- To know the function of platelets
- To learn about different types of inherited and aquired platelet quantitative and qualitative defects.
- To know about the diseases associated with (i) a failure of platelet production and (ii) a shortened platelet lifespan.
- To know the main sequence of events in the coagulation pathways
- To understand normal fibrinolysis and the principles of fibrinolytic therapy
- To know the principles of different coagulation tests.

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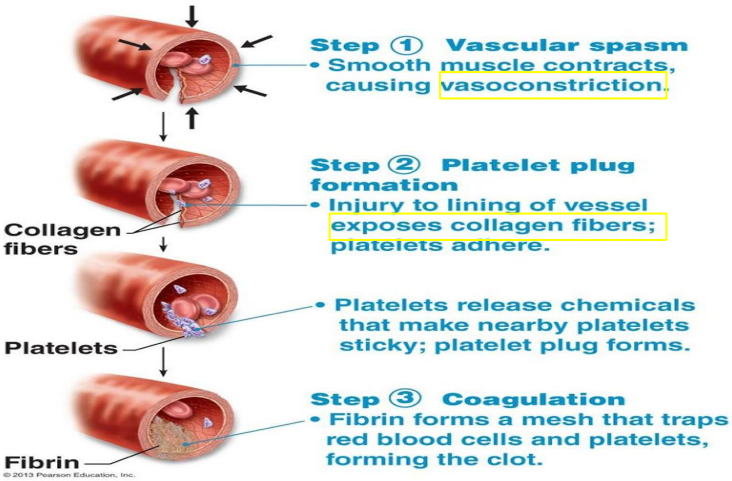
Impotent
Notes
Doctor's slides

3 steps of normal hemostasis

Goal : clot formation



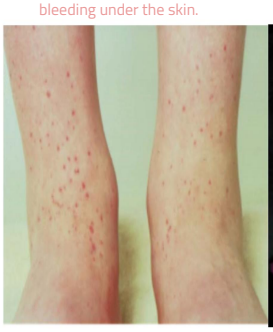
Classification of haemostatic defects

- Bleeding arise from defects in one of the **three** processes:

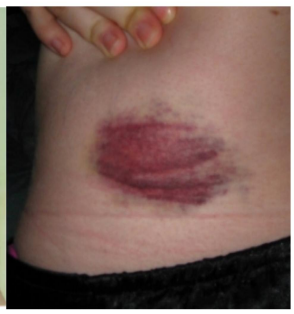
1. **Thrombocytopenia** (a **low platelet** present with bleeding into count [1]) (the commonest cause).
2. **Abnormal platelet function** [2]
3. **A defect in the clotting mechanism (the second commonest cause).**

- clotting defects usually present with bleeding[3] into the deep tissues (muscles and joints).
- Platelet defects usually present with mucocutaneous bleeding.[4]

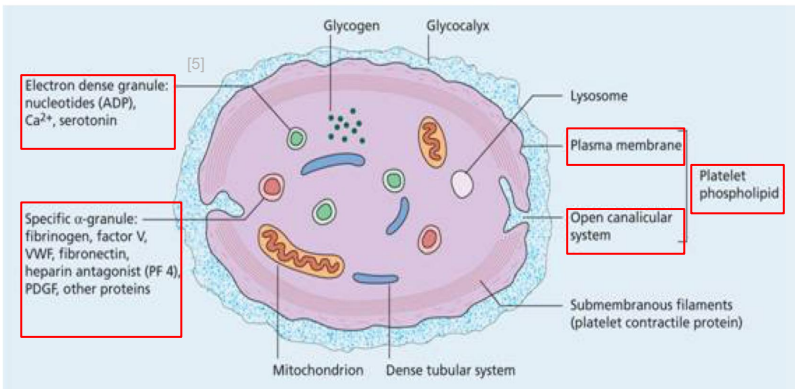
Petechiae
Small pinpoint purple bleeding under the skin.



Ecchymoses
Large purple spot under the skin.



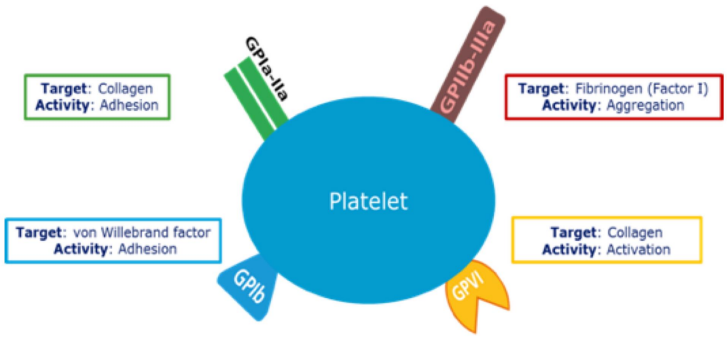
Platelet structure



المحدد بالأحمر اللي ركزت عليه د.فاطمه ..
you should know the content of granules (alpha and electron dense)

[1] by CBC .
[2] the blood count will be normal .
[3] bleeding the main manifestation.
[4] there are two types of bleeding , 1) superficial bleeding which related to platelet count and function .. 2) deep bleeding which related to clotting factors deficiency.
[5]the absent or reduce in the granules either dense or a- granule is called platelet storage pool disease

- The plasma membrane of a platelet contains **glycoproteins (GPs) that are important in the interaction of platelets with subendothelial connective tissue and other platelets.**
- **GP Ia** and **VI**, which bind to **collagen**.
- **GP Ib**, which binds to **von Willebrand factor**[4](**VWF**) and **GP IIb/IIIa**, which binds to **fibrinogen**.



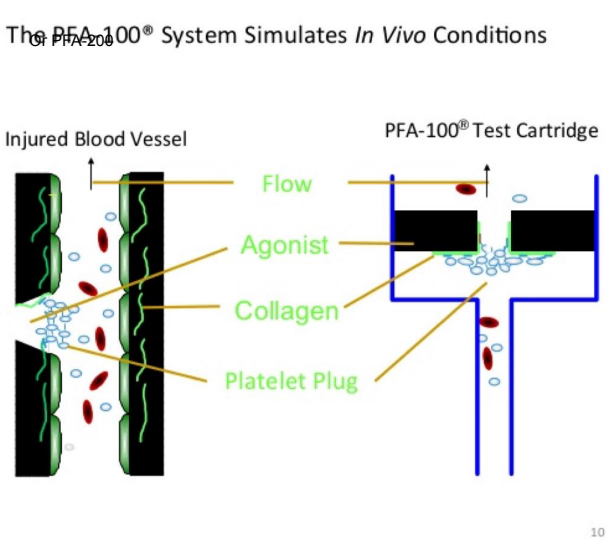
Platelets

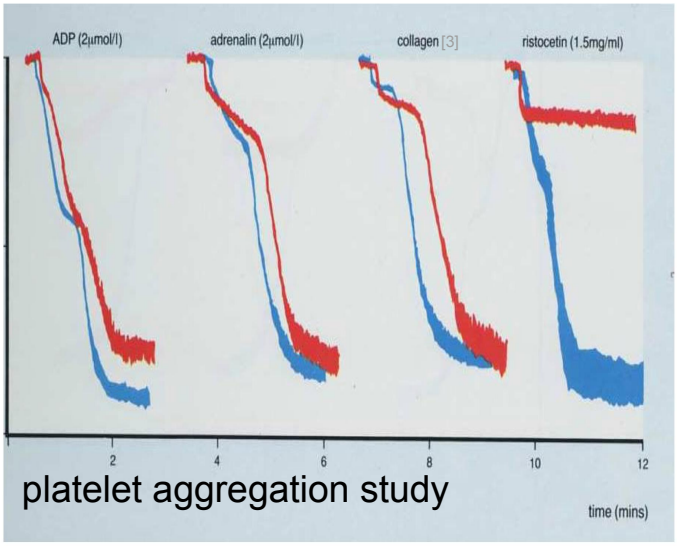
- **Formed in the bone marrow** by the fragmentation of megakaryocyte cytoplasm.
- Their concentration in normal blood is 150-450 X 109/L[1].
- The lifespan of the platelet around **10** days, if a person using aspirin and wanted to have a surgery we stop before **10** days .

Tests of platelet function

Bleeding time	• **Old** method not used in routine practice • It is estimated by making small wounds in the skin of the forearm after applying a blood pressure cuff to the upper arm and inflating it to 40mmHg; the average time that elapses until bleeding ceases is then measured.
PFA-100[2]	• The bleeding time has largely been replaced by an in vitro estimation of primary haemostasis using a machine called a PFA-100.
Platelet aggregation studies	• The **most common is light transmission aggregometry**. • The aggregation of platelets is studied following the addition of substances such ADP, epinephrine, arachidonate, collagen and ristocetin to platelet-rich plasma[3] • Aggregation causes an increase in the light transmitted through the sample and the test is performed using special equipment capable of continuously recording light transmission.

[1] same in adult and children .
[2]platelet function analysis PFA-100 —> الشيء المهم تعرفون ان هذا التست هو اللي يستخدم الان
[3] normally will react with all substances .. if it's not response will gives a flat line.
[4] VWF synthesized outside liver





Thrombocytopenia

- Low platelet count.

Table 14.1 Some causes of thrombocytopenia.

Failure of platelet production

- Aplastic anaemia [1]
- Drugs
- Viruses
- Myelodysplasia
- Paroxysmal nocturnal haemoglobinuria
- Bone marrow infiltration (carcinoma, leukaemia, lymphoma, myeloma, myelofibrosis, storage diseases including Gaucher's disease, osteopetrosis)
- Megaloblastic anaemia due to B12 or folate deficiency
- Hereditary thrombocytopenia (e.g. thrombocytopenia with absent radii, grey platelet syndrome, Bernard-Soulier syndrome, Wiskott-Aldrich syndrome)

Shortened platelet survival

Immune

- Autoimmune (idiopathic) thrombocytopenic purpura
- Secondary autoimmune thrombocytopenic purpura [2] (SLE and other collagen diseases, lymphoma, chronic lymphocytic leukaemia, HIV infection)
- Drugs
- Post-transfusion purpura
- Neonatal alloimmune thrombocytopenia
- Thrombotic thrombocytopenic purpura (most cases)

Non-immune

- Disseminated intravascular coagulation (p. 127)

Increased splenic pooling

[1] the most common cause of failure of platelet production, the aplastic anemia is shut down of bone marrow .
[2] the most common cause of shortened platelet survival.
[3] the aspirin cause defect in collagen.

Immune thrombocytopenic purpura (ITP)

- ITP is characterized by **thrombocytopenia and mucocutaneous bleeding** .
- Acute or Chronic form.

Acute ITP

- Most common **before the age of 10 years** but can affect any age
- Commonly preceded by viral infection (e.g. upper respiratory tract infection, chicken pox, measles).
- Platelet counts are often **less than 20 X 109/L.**
- in most patients has a self-limiting course of 2-4 weeks.
- In approximately 20% it becomes chronic (lasts more than 6 months).
- The **mortality is low**, the main danger being intracranial bleeding.
- You can give platelet if needed.

Chronic ITP[1]

- This occurs mainly in the **age period 15-50 years.**
- Higher incidence in women than in men.
- Platelet counts are **usually between 20 and 80 X 109/L.**
- Spontaneous cures are rare and the disease is characterized by **relapses and remissions.**

[1] the doctor say is is more than 3 months

Diagnosis

- **Children** with the appropriate clinical features, acute thrombocytopenia with large platelets (high MPV) and an otherwise normal blood count (i.e. **no evidence of acute leukaemia**).
- In ITP, bone marrow megakaryocytes are normal or increased in number (up to four- or eightfold) and increased in size.
- An absence or reduction of megakaryocytes rules out the disease.

- Over 80% of patients **recover without any treatment**.
- **Corticosteroids** are widely used
- High dose of **intravenous immunoglobulin** (Ig) cause a rapid increase in the platelet count. [they always start with it , if the platelet count very low!]

- usually not needed in patients with platelet counts above 30-50 X 109/L who have no significant spontaneous bleeding.
- High-dose corticosteroid therapy increases the platelet count to more than 50 X 109/L
- Splenectomy, thrombopoietin receptor agonists, and rituximab are reserved for refractory cases.

Thrombotic thrombocytopenic purpura (TTP) Important

- In healthy individuals a VWF-cleaving protease (ADAMTS 13) VWF.
- In the **absence of the protease** (Inherited or acquired), ultra-large VWF multimers are released that **lead to platelet aggregation** and the disease known as 'thrombotic thrombocytopenic purpura' (TTP).
- This is a serious illness characterized by widespread arteriolar platelet thrombi leading to fragmentation of red cells (schistocytes), thrombocytopenia, neurological symptoms and renal impairment.
- **Coagulation tests are NORMAL.**
- Treatment is by plasma exchange.
- **Platelet transfusion is CONTRAINDICATED** .
- HUS[1] (hemolytic uremic syndrome) is a similar condition affecting children after infection by Escherichia coli or Shigella dysenteriae and treated conservatively.

Increased splenic pooling (or hypersplenism)

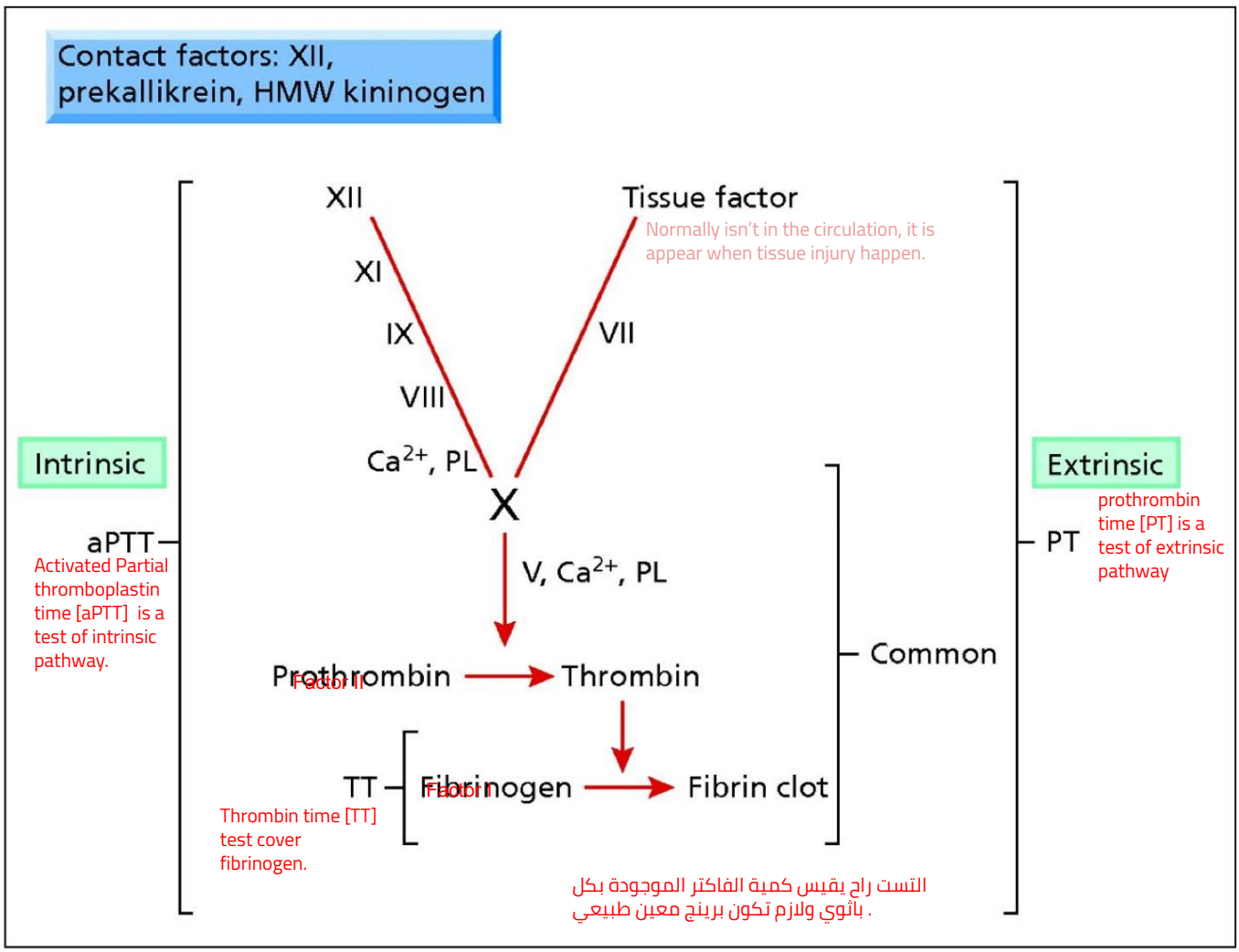
- A normal spleen contains within its microcirculation about 30% of all the blood platelets.
- The splenic **platelet pool increases with increasing splenic size**[2]**,** so that in patients with moderate to massive splenomegaly it may account for 50-90% of all blood platelets, thus causing thrombocytopenia.

platelet disorders

Acquired (Abnormalities of platelet function)	Causes: • Drugs (aspirin and other antiplatelet drugs). • Chronic myeloproliferative disorders. • Myelodysplastic syndromes. • Paraproteinemias (e.g. myeloma or Waldenström's macroglobulinemia) • **Uraemia**.
Inherited	**Glanzmann's disease:** • Rare but severe platelet disorder caused by a lack of glycoprotein IIb/IIIa receptors. • Autosomal recessive. • **Platelets are normal in morphology and number.**
	Bernard-Soulier disease: • Caused by a lack of glycoprotein Ib receptors. • Autosomal recessive. • **Platelets are larger than normal and usually the platelet count is reduced.**
	Storage pool diseases: • These are inherited group of disease resulting in defective platelet granules.

[1] differential diagnosis.
[2] السبلين تخزن ٣٠% من الصفائح , في هذي الحالة لما يزيد حجمه وتخزن اكثر من ٥٠% حيكون الناتج —> thrombocytopenia

Coagulation cascade



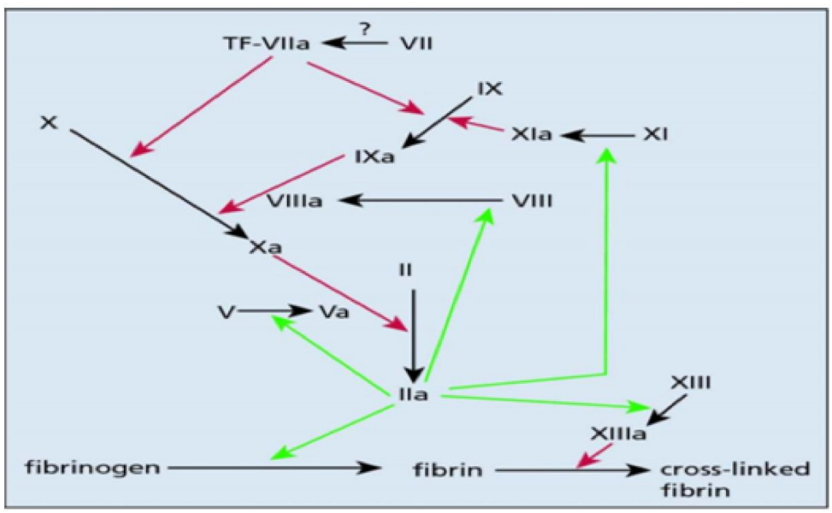


Figure 14.4 Pathways involved in fibrin generation after the activation of coagulation *in vivo* by TF. The suffix 'a' denotes the active form of each coagulation factor. *Notes:* Green arrows – actions of thrombin; red arrows – actions of other active enzymes; dashed blue arrows – inhibition.

The fibrinolytic mechanism

- After haemostasis has been achieved, the body has a mechanism for the enzymatic lysis of clots.
- The dissolution of the fibrin into fibrin-degradation products (FDPs) is carried out by the proteolytic plasma enzyme plasmin.
- Plasmin is present in the plasma in an inactive form.
- **D-dimer is a measurement of fibrin degradation products.**

D -dimer

- D-dimers are raised in thrombosis.
- **It has a high negative predictive value.**
- D-dimers are raised in a variety of clinical situations and so have a low positive predictive value for thrombosis , so it have a negative predictive value.

They can be raised in:

- Pregnancy.
- Malignancy.
- Infection.
- **DIC**.
- Vaso-occlusive sickle cell crisis.
- Surgery.
- Burns.
- Liver disease.
- Snake bites.
- Atrial fibrillation.
- Renal failure.
- Cardiac failure.
- **Venous thromboembolic disease [VTED].**
- Aortic dissection.

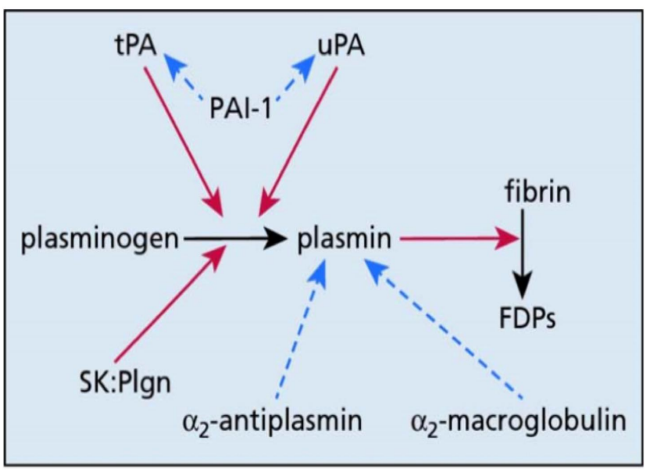
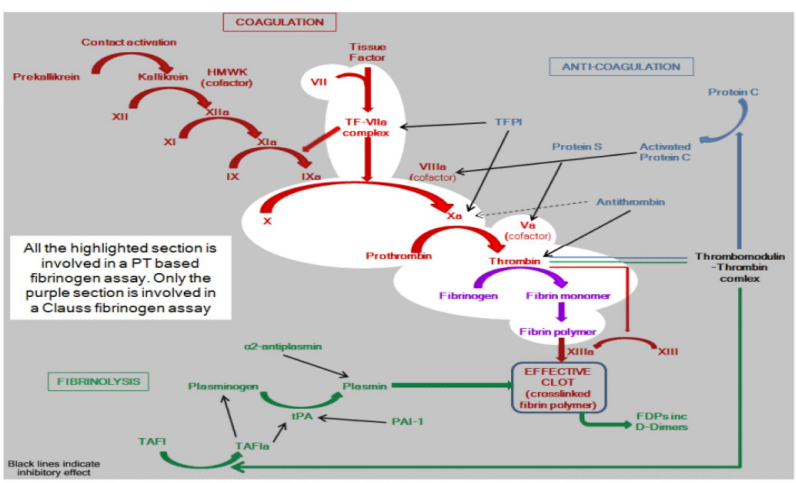


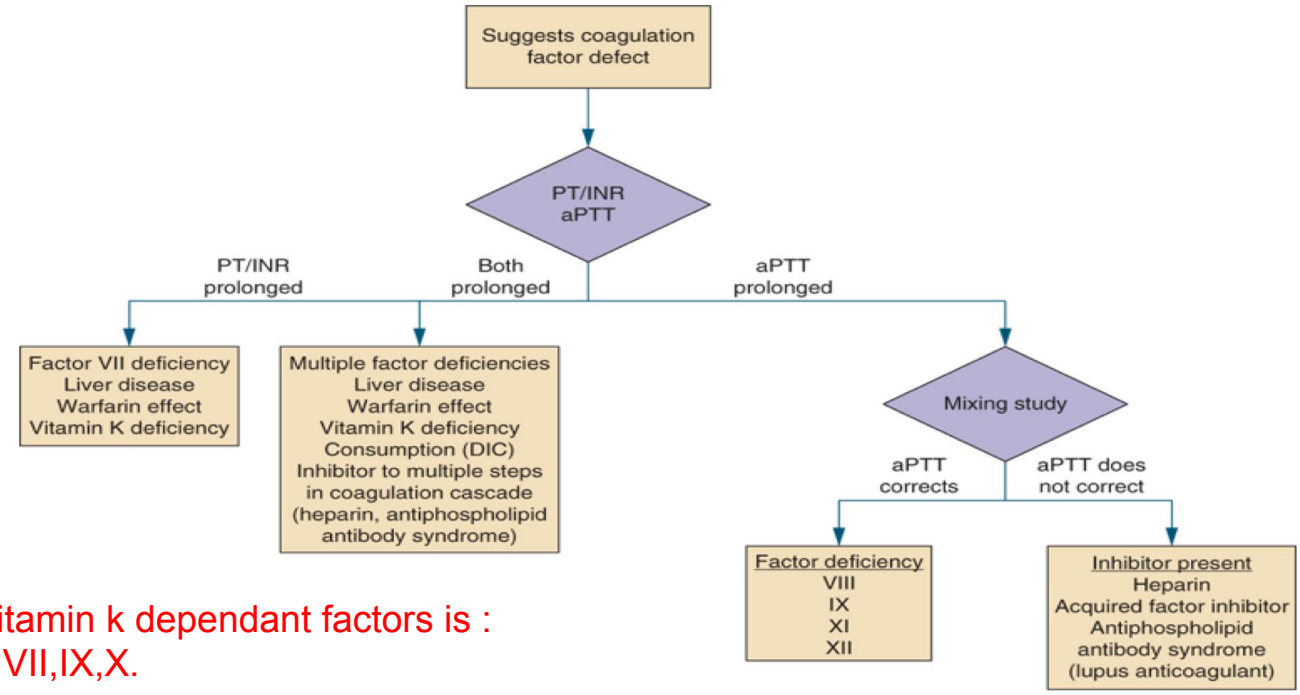
Figure 14.6 The fibrinolytic mechanism.

Coagulation tests

- PT(INR),APTT.
- Fibrinogen.
- D-Dimer.
- Factors Assay.
- Mixing study.
- VWF test.



Very important



Vitamin k dependant factors is :
II,VII,IX,X.

aPTT, activated partial thromboplastin time; CAD, coronary artery disease; DIC, disseminated intravascular coagulation; GI, gastrointestinal; INR, international normalized ratio; ITP, idiopathic thrombocytopenia purpura; NSAIDs, nonsteroidal antiinflammatory drugs; PT, prothrombin time; TTP, thrombotic thrombocytopenic purpura.

In liver disease Factor VII is the first to decreased

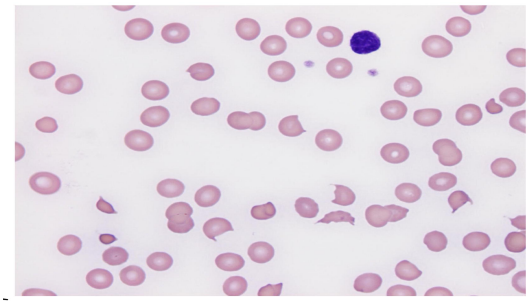
Dr.Fatmah said , it is enough to understand this table

INR	aPTT	TT/Fib	Platelets	Disorders
↑	N	N	N	Liver disease Vit K def Coumadin [warfarin] . Factor VII
N	↑	N	N	Heparin Antiphospholipid Ab Factor VIII, IX, XI von Willebrand's (Factor XII)
N	N	↓	N	Hypofibrinogenemia Dysfibrinogenemia Thrombin Inhibitors Heparin
N	N	N	↓	ITP TTP/HUS Drugs Bone Marrow Splenomegaly

there is defect in fibrinogen .

Case

- A 30-year-old woman is admitted through A & E with a 2 days history of easy bruising, upon admission she had convulsion.
- The LDH is elevated at 2389 U/dL.
- The creatinine is raised at 389 µmol/mL.
- A blood film is shown.



Test	Patient	Reference Range
Hb	7.6 g/dL	11.5-13.5g/dL
WCC	11.9 x 10^9/L	4 -11 x 10^9/L
Platelets	10 x 10^9/L	150 - 400 x 10^9/L
PT	13s	11-14s
APTT	35.6s	23-35s
Fibrinogen	2.1g/L	1.5-4.0g/L

- What is the diagnosis? **TTP.**
- Are there any additional tests you would request?

➢ **ADAMTS 13 (low).**

➢ **Assay for antibodies of protease enzyme (high).**

Test	Patient	Reference Range
ADAMTS13 Activity	<5%	66-126%
ADAMTS13 Inhibitor Assay	28 AU/mL	<11 AU/mL

- What is the treatment in this disorder? **plasma exchange**

Quiz

Q1) In which of the following structures in an adult you will most likely see fragmentation of megakaryocytes?

A) Spleen
B) Bone marrow of the skull
C) Liver
D) Bone marrow of femur

Q2) A gastric glands destruction may more likely lead to

A) Thrombocytopenia
B) Aplastic anemia
C) Immune mediated platelets destruction
D) None

Q3) Which form of thrombocytopenia is more seen in children aged 12 years old?

A) Acute ITP
B) Chronic ITP
C) Neonatal Alloimmune thrombocytopenia
D) Bone marrow suppression

Q4) During your shift at the ER, a couple came in rush with their unconscious baby. After taking history and performing examination, you decided to do CT scan of his brain. CT scan showed hyperdense lesions suggesting intracranial hemorrhage. What is your diagnosis if a wide spread bruises were found in the baby body and a history of chickenpox infection followed by episodes of spontaneous epistaxis?

A) A complicated form of acute ITP
B) Neuroblastoma
C) Chronic ITP
D) DIC

Q5) In the absence of vWF-cleaving protease, which of the following will be released?

A) Collagen
B) Ultra-fibrinogen
C) Ultra-large vWF multimers
D) vWF monomers

Q6) This mineral is required for coagulation

A) K
B) Ca
C) Zinc
D) Copper

Q7) Along with thrombosis, D-dimers can be raised with:

A) Valvular heart disease
B) NSAIDS induced Peptic ulcer
C) Bug bites
D) Atherosclerosis

1) B
2) A
3) B
4) A
5) C
6) B
7) A