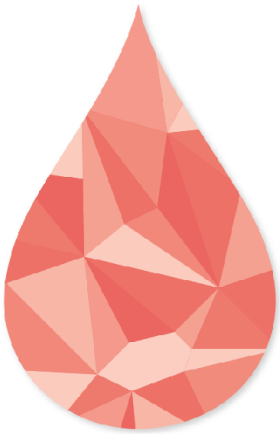


4- approach to bleeding disorders.

= Haematology 435 =

إن أحسنا فمن الله عزوجل, وإن أخطأنا فمن أنفسنا والشيطان.
نظراً لشمولية العمل لمحاضرات الطلاب والطالبات بإمكانكم اعتماده كمصدر للمذاكرة

❖ Learning objectives:

- To know the function of platelets and the relationship between the platelet count in peripheral blood and the extent of abnormal bleeding.
- To know about the diseases associated with:
  1-a failure of platelet production.
  2-a shortened platelet lifespan, especially immune thrombocytopenic purpura (ITP).
- To know the principles of investigation of patient suspected of having a haemostatic defect.
- To understand the role of platelets, blood vessel wall and coagulation factors in normal haemostasis.
- To know the classification of haemostatic defects.
- To know the platelet morphology and life span.
- To know the platelet function and diseases due to platelet function disorders.
- To know the causes of thrombocytopenic purpura and non-thrombocytopenic purpura.

➢ Color Codes:

- Pink: Girls' notes. Blue: Boys' notes. Red: Important Notes. Gray: Extra notes.
- Purple: Lecture notes & Pathoma notes.

➢ References:

- Girls&Boys Doctors Slides and Notes.
- Lecture notes pathology (chapter 12)
- Pathoma (chapter 5)
- Team 434 & 433.

Revised by
خولة العماري & هشام الغفيلي

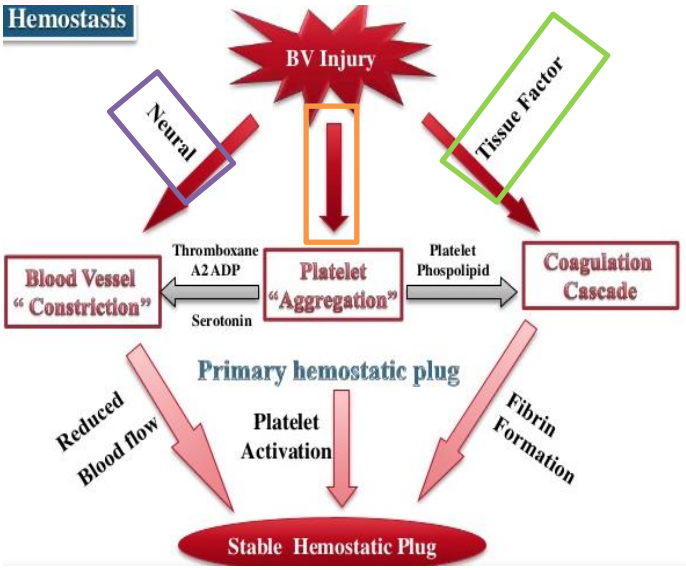
➢ Correction File: (HERE)

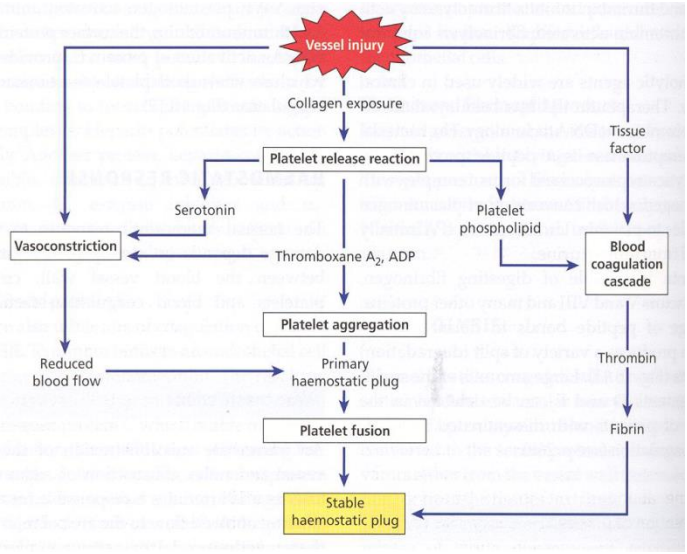
You can skip this if you understand physiology

❖ Physiology of platelets:

Function of platelets:

- Formation of a haemostatic plug at sites of damage to vascular endothelium.
- The platelets are also stimulated to produce the **prostaglandin**, and **thromboxane A2** from arachidonic acid derived from the cell membrane.
- The release of ADP and thromboxane A2 causes an interaction of other platelets with the adherent platelets and with each other (secondary platelet aggregation), thus leading to the formation of a platelet plug (primary haemostasis).
- At the site of injury, tissue factor (TF) is expressed and the TF-VIIa complex initiates the formation of a fibrin clot within and around the platelet plug (secondary haemostasis)
- Platelets are also responsible for the contraction of the fibrin clot once it has been formed.





When injury happens to a Blood Vessel:

- **Tissue Factor** will be released and starts the coagulation cascade, when it is disseminated, fibrin will form, which is very important for a stable plug.
- **Activated platelet** will lead to aggregation which creates the primary hemostatic plug which leads to secretion of granules from inside the platelet which makes a more stable plug.
- **Neural stimulation** leads to BV contraction which reduces blood flow to stop bleeding.

For all these to happen, the vessel has to be normal and well, with normal platelet and anti coagulation factors.

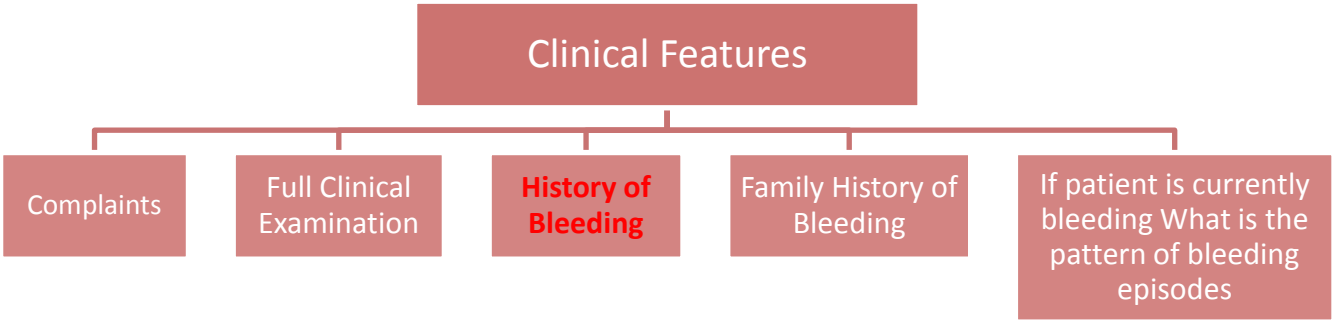
- **Needed Lab Tests to make sure of these:** BT (bleeding time), CBC, Plt (platelet) count, PT (prothrombin time) , PTT (Partial thromboplastin time)
- **Platelet Study:** Morphology, Function, Antibody.

❖ Normal Haemostasis:

The cessation (stopping) **of bleeding following trauma to blood vessel is result from three process:**

1. The contractions of vessel walls.
2. The formation of the platelets plug at the site of the break in the vessel wall
3. The formation of a fibrin clot within and around the platelet aggregates.

❖ Investigations of Bleeding Disorders:



❖ Classification of Hemostatic Defects:

The action of platelets and the clotting mechanism are closely intertwined in the prevention of bleeding. However, bleeding arise from defects in one of the three processes:

1) Thrombocytopenia (a low platelet count) ← **the most common cause**.
2) A defect in the clotting mechanism (clotting factors) ← **second most common cause.**
3) Abnormal platelet function (the count of platelets is normal)

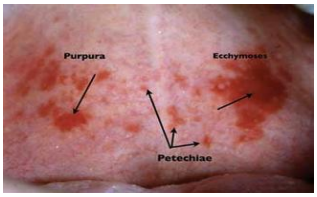
❖ Clinical Distinction:

Clinical distinction can frequently be made between bleeding due to platelet defects (in number or function) and clotting factors defects (coagulation defects) .

Disorders of primary hemostasis		Disorders of secondary hemostasis	
Usually due to **abnormalities in platelets or vessel wall defects**		Usually due to **coagulation factors** abnormalities	
Clinical features include **mucosal and skin** bleeding		Clinical features include **deep** tissue bleeding	
Mucosal bleeding (epithelial surface of the nose, uterus and other organs)	Superficial bleeding into the **skin**	**muscles**	**joints**
Epistaxis (the most common symptom)	Petechiae , purpura and ecchymoses. ***	(Haematomas*)	(haemarthorosis**)
This is called **mucocutaneous bleeding**		This is called **musculoskeletal bleeding**	

*a solid swelling of clotted blood within the tissues.
**is a bleeding into joint spaces. It is a common feature of Hemophilia.

***The difference between them:
Petchechiae (1-2mm), purpura (>3mm), eccymoses (>1cm)



When platelets are below 50 *X* 10^9/L. (At levels between 20 and 50 *X* 10^9/L)	When platelets are below 20 X 10^9/L **(severe)** (**gross** haemorrhage)
Petechial haemorrhages and ecchymoses and bleeding from other sites may occur. **petechiae, ecchymoses and nose bleeds are the commonest symptoms**	(melaena, haematemesis, haematuria) becomes increasingly common

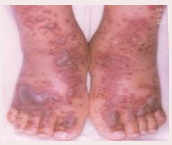
❖ Hereditary and aquired vascular disorders:

المطلوب منكم هنا إنكم تعرفوا الأسماء

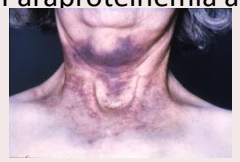
The ones in red are important.

Acquired Vascular Disorders

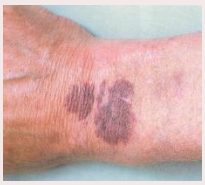
- Allergic purpura (Henoch-Schonlein purpura)



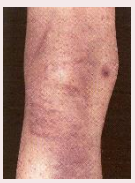
- Paraproteinemia and amyloidosis.



- Senile purpura (it's normal to have it in old age)



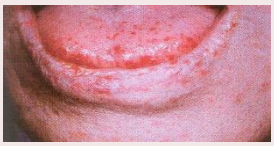
- Drug-induced vascular purpuras (Steroid therapy, sulfonamides, iodides, aspirin, digoxin, methyldopa, estrogen, allopurinol, penicillin and other antibiotics).
- Vitamin C Deficiency (Scurvy) →



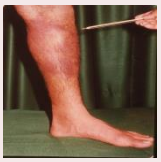
- Purpura simplex (Easy brusability)
- Psychogenic purpura
- Purpura associated with infections.

Hereditary Vascular disorders

- Hereditary Haemorrhagic Telangiectasia (Rendu-weberosler syndrome) (bleeding in tongue and lips)



- Kasabach-merritt syndrome (Haemangioma – Thrombocytopenia)
- Ehlers-Danlos syndrome (more common in lower limbs) →



- Pseudoxanthoma elasticum
- Homocystinuria
- Marfan syndrome
- Osteogenesis imperfecta

But if you have time, be a good Med student and read up on these disorders. ☺
Feed your brain.
Grow in Knowledge.

❖ The Platelets:

Normal Platelet Count	Normal Platelet Size MPV
150 – 450 X 10^9 /L	7.2 – 11.1 fl

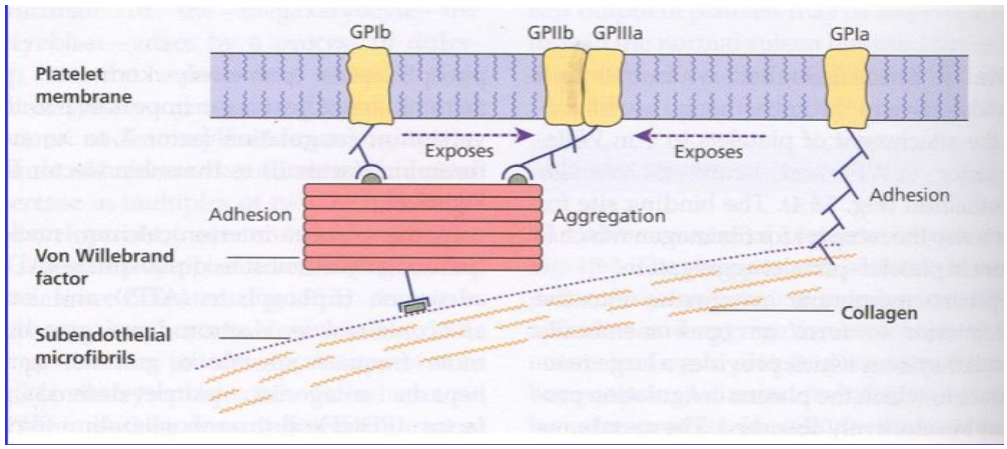
Formation of Platelet is by Segmentation of the cytoplasm of the **megakaryocyte** in the bone marrow

Normal Platelet Diameter	Normal Platelet Life Span
1 – 3µ	**7 – 10 days**

❖ Platelet Activation:

What happens to the platelet after if gets activated i.e. after we started bleeding?

- Stickiness
- Shape Change
- Internal Contraction
- Secretion



There are Glycoproteins (GP) on the Platelet membrane that are important for the attachment of the platelet to the sub-endothelial micro fibrils on the collagen.
GPIb, GPIIb, GPIIIa, *do not* attach *directly* to the collagen. (adhesion and aggregation)
However, GPIa adheres *directly*. (adhesion only)

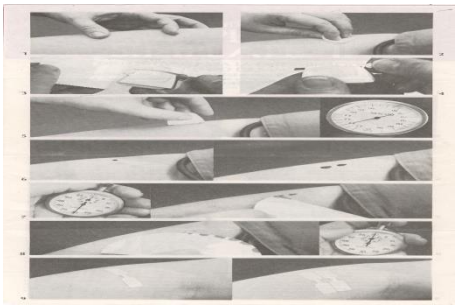
It's important to know the functions of the GPs. *check the Physiology team, we're sure they made a great job explaining it!*

The glycoprotein	GP1a (GPVI)	GPIb	GPIIb-IIIa
Attached to	Collagen (directly)	To collagen via von willebrand factor (indirectly)	It is a receptor for fibrinogen and von Willebrand factor
Function	adhesion	adhesion	aggregation
Deficiency	-	Bernard-soulier syndrome	Glanzmann thromsdthenia

❖ Measurements of Platelet Function:

➢ Tests of Platelet Function Bleeding Time: (the old way)

The bleeding time 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. Normal bleeding time is 3 – 8 mins



➢ PFA - 100 / PFA – 200

(The new way) (PFA = Platelet function analyser)

The bleeding time has largely been replaced by an in vitro estimation of primary haemostasis using a machine called a PFA-100. PFA – 200 is the newest device.

❖ Platelet Aggregation:

➢ Platelet Aggregation Studies:

-The most common is **light transmission aggregometry**, whereby the aggregation of platelets is studied following the addition of substances such as: ADP, epinephrine, arachidonate, collagen and Ristocetin* to plateletrich plasma.

-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.

يعني تخيلوا كأس زجاجي مليانة صفائح دموية، وأخذنا مصباح ووجّهنا النور عليها، لأن الكأس مليانة، ما راح تمر النور من خلاله. ولكن أول ما نحط واحد من المواد اللمذكورة هنا ← في كأس الصفائح، بيتجمعون (يتخثرون) ويسوون كتلة وحدة، وبالتالي النور راح يمر من خلال بقية السائل المتبقي.

* **Ristocetin**, an antibiotic that causes vWF and platelets to stick together, is then added to the plasma. In the presence of **ristocetin**, blood with adequate vWF clots normally. Blood that's deficient in vWF or has defective vWF won't clot. As in Bernard-soluier syndrome.

Multiple Electrode Aggregometer →

❖ Inherited disorders of platelets function:

Membrane abnormalities (important)	**-Bernard-soluier syndrome.** **-Thrombsthenia (Glanzmann's disease).** -Platelet factor-3 deficiency. you should know that these are membrane abnormality
Intracellular abnormalities	-
Storage-pool (dense body) deficiency. (important)	-Hermansky-pudlak syndrome. -Wiskott-aldrich syndrome. -Chediak-higashi syndrome. -Thrombocytopenia with absent radii. -Idiopathic storage-pool disease.
Storage pool (alpha-granule) deficiency (important)	-Gray platelet syndrome.(common and most popular) -Combined deficiency of dense bodies and alpha granules.
Defect of thromboxane synthesis.	-Cyclo-oxygenase deficiency. -Thromboxane synthetase deficiency. -Defective response to thromboxane.
Miscellaneous.	-Epstein's syndrome. -May-hegglin anomaly.

❖ **Membrane abnormalities: "very important"**

Glanzmann's disease:

This is a rare but severe platelet disorder caused by a lack of **glycoprotein IIb/IIIa receptors**.
Inheritance is autosomal recessive

-platelets are normal in morphology and number.
(impairment in platelets aggregation)

Bernard-soulier disease:

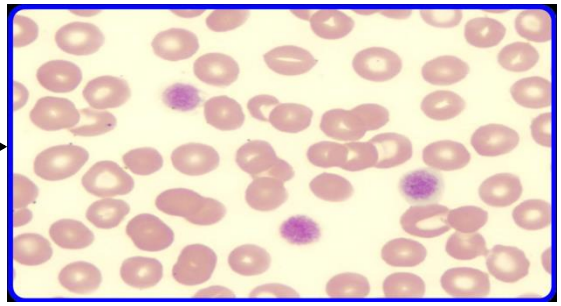
This is a platelet disorder caused by a lack of **glycoprotein Ib receptors**.
Inheritance is autosomal recessive.

-Platelets are larger than normal and usually the platelet count is reduced.
(impairment in platelets adhesion)

❖ Inherited disorders of platelets function in platelets aggregation test.

	ADP	Collagen	Arachidonate	Ristocetin
Normal	reaction	reaction	reaction	reaction
Thrombasthenia	no reaction (linear)	no reaction (linear)	no reaction (linear)	reaction
Bernard – Soluier syndrome	reaction	reaction	reaction	no reaction (linear)

Blood film picture from a patient with **Bernard-Soulier syndrome** showing very large platelets **(giant platelets).**



❖ Acquired disorders of platelets function:

- **Uremia.** (uremia disrupts platelet function; both adhesion and aggregation are impaired.
- Myelodysplastic syndrome.
- Chronic Myeloprolifrative disorders.
- Paraproteinemias (e.g. ,myeloma or Waldenstrom's macroglobulinemia)
- **Drugs (aspirin** and other antiplatelets drugs**).**
- **Scurvy.**
- Severe burns.
- Valvular and congenitaal heart dises.
- Acute leukaemias and pre-leukaemic states.
- Liver disease .
- Chronic hypoglycemia .
- Dysproteinaemias.

❖ Causes of Thrombocytopenia:

❖ Bone marrow failure:

- Failure of platelet production
-Selective megakaryocyte depression
-Rare congenital defects
-drugs, chemicals, viral infections
-Part of general bone marrow failure
-cytotoxic drugs
-radiotherapy
-aplastic anemia, Megaloblastic anemia
-leukemia
-Myelodysplastic syndromes
-myelofibrosis
-Marrow infiltration e.g. carcinoma, lymphoma
-Multiple myeloma
-HIV infection

❖ Increased consumption of platelets in the peripheral blood:

1-Immune:

-autoimmune (idiopathic)
-associated with systemic lupus erythematosus, chronic lymphocytic leukemia or lymphoma.
-feto-maternal alloimmune thrombocytopenia.
-post- transfusional purpura

2-infections: HIV, other viruses, malaria

3-drug-induced: (heparin induced thrombocytopenia)

4-Disseminated intravascular coagulation

5-Thrombotic thrombocytopenic purpura (explained in the next slide)

6-Abnormal distribution of platelets:

-Splenomegaly. (explained below)

7-Dilutional loss:

-Massive transfusion of stored blood to bleeding patients

Increased splenic pooling:

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

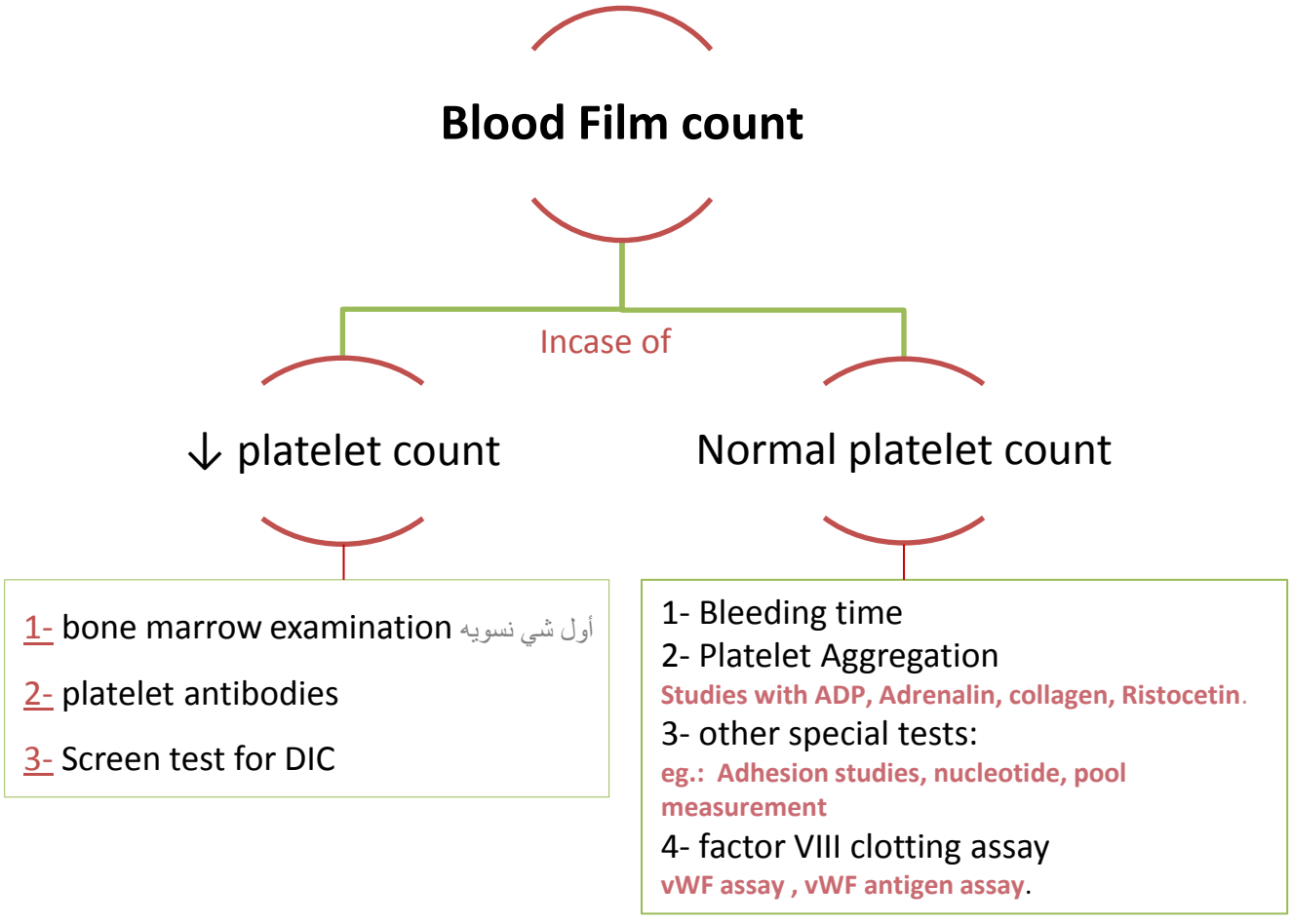
Thrombotic thrombocytopenic purpura (TTP): read it just in case

I-n healthy individuals a VWF-cleaving protease (ADAMTS 13) cleaves the Tyr 842-Met 843 peptide bond in VWF to produce the characteristic multimer profile.

-In the absence of the protease, 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, thrombocytopenia, neurological symptoms and renal impairment**.

❖ Blood Count Film:



Thrombotic thrombocytopenic purpura (TTP) & Hemolytic uremic syndrome (HUS): read it just in case.

Clinical features

- Fever.
- Thrombocytopenic purpura.
- Hemolytic anemia.
- Neurological symptoms
- Renal dysfunction

causes

- Genetic predisposition.
- It associates with other condition
- Infections (E.coli type 0157, Shigella dysenteriae serotype 1, and viral infection).
- Hypersensitivity.
- Oral contraceptive.
- Autoimmune diseases
- e.g. SLE , rheumatoid arthritis, Rheumaticd , Spondylitis, polyarthritis Nodosa, Sjorgen's syndrome
- Chemotherapy.
- e.g. Mitomycin, Cisplatinum, Bleomycin, Vindestine, Vinblasine, Doxorubicin, Vincristine, Asparaginase, prednisone, cyclosporine.

Thrombocytopenia

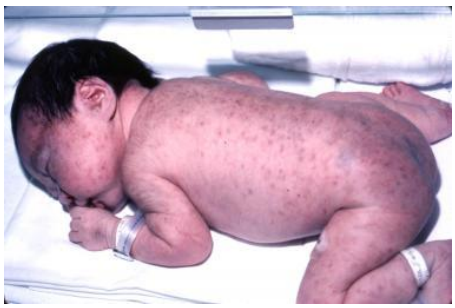
Immune thrombocytopenia

1- Clinical features:

Degree of thrombocytopenia	symptoms	Physical findings
Mild (>50 000/mm3)	None	None
Moderate (30,000-50,000/mm3)	Bruising with minor trauma	Scattered ecchymosis at trauma site
Severe (10,000-30,000/mm3)	Spontaneous bruising menorrhagia	Petechiae and purpura, more prominent on extremities.
Marked (<10,000mm3)	1-Spontaneous bruising 2-Mucosal bleeding 3- risk of **CNS bleeding**	1-Generalized purpura 2-Epitaxis 3-GU bleeding 4-CNS symptoms

2- Laboratory features: read it just in case

1- Thrombocytopenia with increased number of **large** platelets . (>3µ)
2- Increased number and size of megakaryocytes.
3- Reduced intravascular platelet survival.
4- Elevated levels of platelet- associated IgG or IgM.



As a result of drugs and toxins

Thrombocytopenia

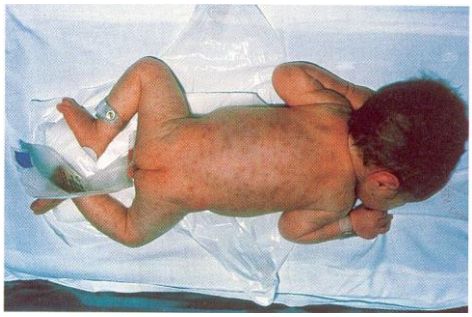
Immune thrombocytopenia

ITP is characterized by petechiae, bruising, spontaneous bleeding from mucous membranes and a reduction in the platelet count. The disease presents in both an acute and a chronic form.

Immune thrombocytopenia purpura

read them just in case

Acute ITP	Chronic ITP
-This is seen at all ages but is most common before the age of 10 years. Two-thirds of patients give a history of a common childhood viral infection (e.g. upper respiratory tract infection, chicken pox, measles) -2-3 weeks preceding the purpura. Platelet counts are often **less** than 20 *X* 10^9/L. -In most patients (80%) the disease runs a self-limiting course of 2-4 weeks, but in approximately 20% it becomes chronic; that is, it lasts more than 6 months. -The mortality is low, the main danger being **intracranial bleeding**.	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 10^9/L. -Spontaneous cures are rare and the disease is characterized by **relapses and remissions.**
Diagnosis:	-Children with appropriate clinical features, acute thrombocytopenia and an otherwise normal blood count (i.e. no evidence of acute leukemia). -In ITP, bone marrow megakaryocytes are normal or increased in number (up to four-or eight folds) and increased in size.



A newborn baby with allo-immune thrombocytopenia showing widespread purpura all over the body.

As a result of drugs and toxins

Thrombocytopenia

Immune thrombocytopenia

Immune thrombocytopenia purpura

Treatment (read them only in case)

Acute ITP	Chronic ITP
Over 80% of patients recover without any treatment. -**Corticosteroids** are widely used. -High doses of intravenous immunoglobulin (Ig) cause a rapid increase in the platelet count.	**1-First line treatment:** Treatment is usually **not** needed in patients with platelet counts above 30-50 X 10^9/L who have no significant spontaneous bleeding. **-High-dose corticosteroid therapy increases the platelet count to more than 50 X 10^9/L** -**Prednisolone** 60 mg/day. -Splenoctomy. **2-second line treatment:** -Azathioprine, cyclophosphamide, danazol, dapsone, cyclosporine A, mycophenolate mofetil and Rituximab have all been used, particularly in patients who fail to respond to splenectomy. -High dose of **intravenous Ig** (e.g. 1 g/kg/day for 2 days) has also been found to **increase** the platelet count to greater than 50 X 109/L in 80% of patients with chronic ITP.

As a result of drugs and toxins

Thrombocytopenia

Immune thrombocytopenia purpura

- Bone marrow suppression
- Predictable (dose-related)

ionizing radiation, cytotoxic drugs, ethanol

- Occasional

chloramphenicol, co-trimoxazole, idoxuridine, penicillamine, organic arsenicals, benzene, etc.

- Immune mechanisms (proven or probable)
- Analgesics, anti-inflammatory drugs, gold salts
- Antimicrobials

pencillins, sulphonamides, trimethoprim, rifampicin

-sedatives, anticonvulsants

diazepam, sodium valproate, carbamazepine

- Diuretics

acetazolamide, chlorathiazides, furosemide

- Antidiabetics

chlorpropamide, tolbutamide

- Others

digitoxin, heparin, methyldopa, oxyprenolol, quinine, quinidine

- Platelet aggregation

Ristocetin, heparin

As a result of drugs and toxins

read them just in case

❖ Platelet transfusion: "in severe cases and severe hemorrhage"

It is often possible to raise the platelet count temporarily by platelet transfusions.

•The main indication for platelet transfusion is **severe hemorrhage** caused by:
1-Thrombocytopenia due to diminished platelet production or DIC.
2-Abnormal platelet function.

Transfusion may also be indicated in a patient with **thrombocytopenia or defective platelet function prior to surgery.**

•Another indication for platelet transfusion is thrombocytopenia (platelets <50 *X* 10^9/L) in patients receiving massive blood transfusions.

•Platelet counts need only be maintained above 10-20 *X* 10^9/L, since severe bleeding is rare above this level.

➢ Check your Understanding! (HERE)

= Haematology 435 =

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Or on twitter