Bleeding Disorders

435 medicine teamwork

[Important | Notes | Extra | Editing file]

lecture objectives:

- Overview of Hemostasis.
- Congenital Bleeding Disorders.
- Acquired Bleeding Disorders.
- Platelet Disorders (Number & Function).
- Approach to the bleeding patients.
- Management of Bleeding patients.

★ I highly advise you to view this 1-page lecture summary before starting the lecture.

Done By: Bedoor Julaidan & Nouf Altwaijri
Edited by: Rahaf Binabbad
Revised By: Luluh Alzeghayer & Ahmed Alyahya
References: Slides - Master the Boards - Essential Haematology- 433 Medicine team

Overview: Hemostasis

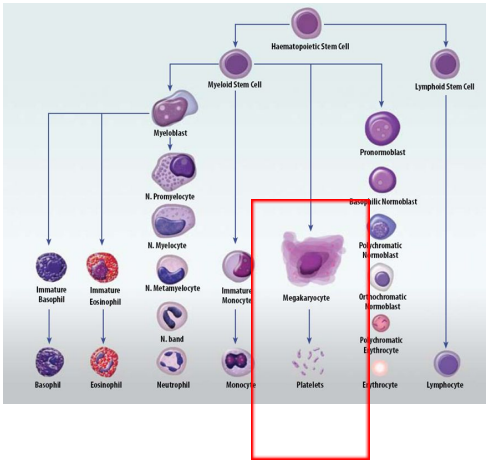
Definition:

- The process through which bleeding is controlled at a site of damaged or disrupted endothelium.

A dynamic interplay between:

- **Cellular** Components: (Platelets & Endothelium)
- **Plasma Proteins** Components: **3** protein systems
  1. Blood Coagulation (Clot Formation)
  2. Fibrinolysis (Clot Lysing)
  3. Anticoagulant (Regulating)

Whenever the vascular integrity is breached (vessel injury) 3 things happen. Firstly, vasoconstriction, secondly platelet plug formation lastly blood clotting (coagulation cascade)



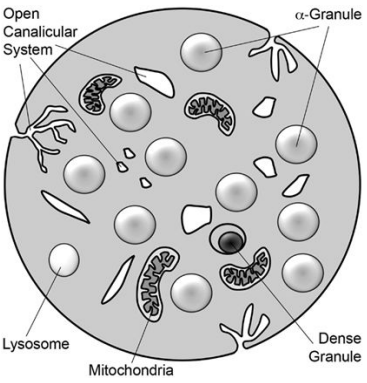
Platelets:

- Produced in the **Bone Marrow** by fragmentation of the cytoplasm of **megakaryocytes**.
-Each megakaryocyte form **1000 to 5000** platelets.
-Time interval from differentiation of the human stem cell to the production of platelets (~ 10 days)
-**Thrombopoietin** → the major regulator of platelets production via c-MPL receptor[1] (thrombopoietin is produced by liver (95%) & kidney)
-Normal platelets counts (150 – 400 x 10^9)
-Platelets life span (**7 – 10 days**)

Platelets ultrastructure: Extremely small & discoid (3 x 0.5 µm in diameter)

Contains 3 types of storage granules:		
α Granules	Dense Granules (δ Granules)	Lysosomes
Clotting Factors **VWF** (von willebrand factor) PDGF[2] IGF1[3]	**ADP & ATP** Serotonin Histamine Ionized Ca	Hydrolytic enzymes

Platelets Functions:



1-**Adhesion** (Platelets stick to the vessel Wall)
-Adhesion is through attachment of **GP Ib-IX-V**[4] to **VWF**
-VWF is synthesized in endothelial cells & megakaryocytes
-VWF is stored in storage granules of endothelial cells & α granules of Platelets
-VWF Rises with stress, exercise, adrenaline, infusion of DDAVP (desmopressin)
2-**Aggregation** (cross linking of Platelets, platelets stick together)
-Aggregation is through attachment of **GP IIb/IIIa** receptors (found on platelets' surface) to **VWF and Fibrinogen** (mainly fibrinogen)
3-**Release Reaction & Amplification** (aggregation formation & stabilization)
-Primary activation by various agonists induces intracellular signaling leading to release of α granules contents (platelets aggregation and stabilization), & ADP (platelets activation) from dense granules

[1] Thrombopoietin receptor
[2] Platelet derived growth factor
[3] Insulin like growth factor
[4] The **GPIb-IX-V complex** is a membrane receptor complex present on the platelet surface.

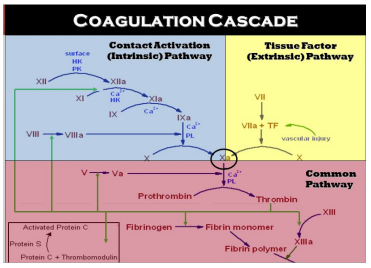
-Formation of Thromboxane A2 by various agonists induces intracellular signaling (potentiates platelets aggregation and causes powerful vasoconstriction).

*normally the platelets don't adhere to the endothelium but when there is injury in the endothelium the circulating vWf will attach to subendothelial collagen on one side, and to **GP Ib** of platelets on the other side. this binding will activate the platelets. When the platelets are activated, they change in shape and receptor becomes activated *normally it is inactive*. Follows that degranulation of platelets' granules → fibrinogen, vWF, serotonin (which causes vasoconstriction), ADP (important for platelets activation and aggregation) and Ca (needed in the secondary hemostasis 'coagulation'). The activated platelets also secretes thromboxane A2 which activates further platelets and causes vasoconstriction. lastly, platelets aggregation mediated by GPIIb/IIIa receptor when it binds to fibrinogen. Many GP IIb/IIIa receptors will attach to single fibrinogen and this what makes platelet plug.

Platelets Inhibitors:

- **Prostacyclin (PGI_2)**
  -Synthesized by vascular endothelial cells
  -Potent inhibitor of Platelets aggregation & causes vasodilation by rising cAMP
  -Prevents Platelets adhesion to normal vascular endothelium
- **Nitric Oxide (NO)**
  -Released from endothelial cells, macrophages, & Platelets
  -Inhibit Platelets activation & promotes vasodilation

Coagulation cascade:



Intrinsic pathway:

We start by factor 12 which activates factor 11. Factor 11 will activate factor 9. Factor 9 in the presence of factor 8 will activate factor 10.

Extrinsic pathway:

We start by factor 3 (tissue factor) that activates factor 7. Factor 7 activates factor 10

Common pathway:

Starting by factor 10 that activates factor 2 (prothrombin) in the presence of factor 5. Prothrombin will activates factor 1 (fibrinogen to fibrin).

-Extrinsic pathway is what gets activated in times of injury. but its activation is not sufficient and we need the intrinsic pathway but how the intrinsic pathway gets activated? when factor 7 activates factor 10 and factor 10 activates prothrombin to thrombin, thrombin will activate intrinsic pathway (thrombin activates factor 5,7,8,11,13). Factor 7 also activates factor 9

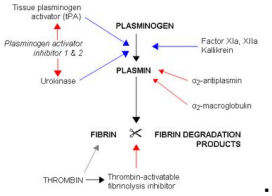
-The whole idea of coagulation cascade is to **generate fibrin**, once we generate fibrin we need to cross-link fibrin molecules **to stabilize platelet plug** in order to form **clot**, and how this happens? by **factor 13, factor 13 enables formation of fibrin mesh 'clot stabilization'.** In factor 13 deficiency (rare bleeding disorder) we give them fresh frozen plasma because we don't have it concentrated.

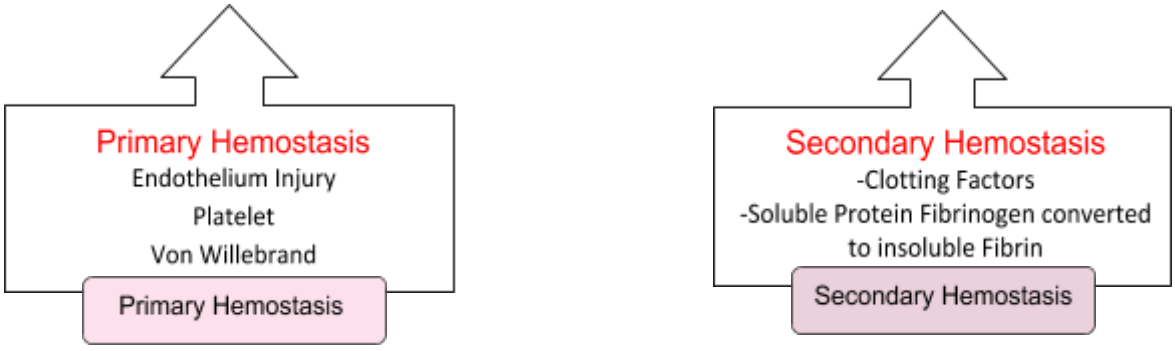
Clotting Factors in Blood and Their Synonyms

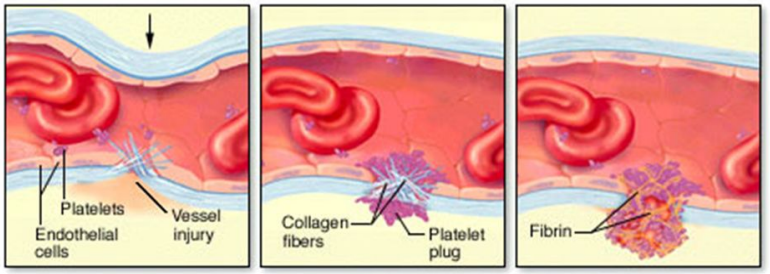
Clotting Factor	Synonyms
Fibrinogen	Factor I
Prothrombin	Factor II
Tissue factor	Factor III; tissue thromboplastin
Calcium	Factor IV
Factor V	Proaccelerin; labile factor; Ac-globulin (Ac-G)
Factor VII	Serum prothrombin conversion accelerator (SPCA); proconvertin; stable factor
Factor VIII	Antihemophilic factor (AHF); antihemophilic globulin (AHG); antihemophilic factor A
Factor IX	Plasma thromboplastin component (PTC); Christmas factor; antihemophilic factor B
Factor X	Stuart factor; Stuart-Prower factor
Factor XI	Plasma thromboplastin antecedent (PTA); antihemophilic factor C
Factor XII	Hageman factor
Factor XIII	Fibrin-stabilizing factor
Prekallikrein	Fletcher factor
High-molecular-weight kininogen	Fitzgerald factor; HMWK (high-molecular-weight) kininogen
Platelets	

-Thrombin is responsible for multiple negative feedback loops that help to control coagulation. one of them is by activating plasminogen to plasmin that breaks fibrin mesh. Thrombin also activates antithrombin that blocks further activation of thrombin and factor 10. At the end of this phase (coagulation cascade) fibrinolysis phase follows.

So in summary:

Hemostatic Phases			
1.Vascular Phase	2.Platelet Phase	3.Plasma Coagulation Phase	4.Fibrinolysis Phase
-Release of locally active vasoactive agents (Endothelin, Thromboxane A2, Fibrinopeptides). -**Vasoconstriction** at the site of injury reduces blood flow.	Platelets Adhesion & Aggregation (via VWF, ADP, TXA2) -Formation of **Platelet Plug**.	-Propagation of the clotting process by the coagulation cascade of coagulation factors. -Formation of **Fibrin Clot.**	-Termination of clotting by antithrombotic control mechanisms & removal of the clot 





★ The main function of the **primary hemostasis** is to form Platelet plug

★ The main function of the **secondary hemostasis** is to form fibrin clot

Hemostasis - Helpful Blood Clotting 4:48 mins

Approach to Patient with Potential Bleeding

Anticoagulants:
The most famous one is warfarin, what's its relation to vitamin K?
its one of the major components of the coagulation factors especially if the patient came to you with coagulopathy and prolonged ptt with normal pt + chronic liver disease with high INR vit k is not soluble because of lack of bile so there is deficiency of factor five and prolongation of INR, so عن k الدكتور ممكن يكون ذكي بس مو كفايه فايش يسوي؟ بيعطيهم فيتامين
طريق الفم بيطلع ما يستفيد منه المريض، لازم تعطونه انجكشن!
مو لازم تعرفون الهافلايف

1/Detailed patient & family medical history (crucial & vital regardless of the prior lab testing)

- Establish likelihood of a bleeding disorder
- Guide laboratory Testing

-Did bleeding occur: •**Early** in the newborn period (circumcision)
•**After hemostatic Challenges** (delivery, injury, trauma, surgery, invasive dental

procedure, menstruation)
-Frequency & pattern
-Duration: •**Onset** (congenital vs. acquired)
•Time required for **cessation**
-Sites of bleeding (specific or multiple):

Sites of bleeding	
Mucocutaneous Bleeding 'Primary Hemostasis Defects (PLT or vW Factor)'	**Deep Tissue Bleeding 'Secondary Hemostasis Defects (Clotting Factors Deficiencies)'**
•Easy bruising •Epistaxis •Menorrhagia	•Joints •Muscles •Central Nervous System

- Current use of medications or **herbal** supplements
- Use of Bleeding Assessment Tools (differentia bleeding phenotypes, require validation by prospective studies)

2/Laboratory Testing:

Screening Tests:

1.**CBC** (Platelet count)
2.**Prothrombin Time (PT)** ⟶ measures **FVII, X, V, II, I** - (normal time 10-14 secs) "extrinsic pathway"
3.**International Normalized Ratio** (INR) ⟶ the ratio of a patient's PT to a normal (control) sample, raised to the power of the ISI (international sensitivity index) value for the control sample used.

$$INR = \left(\frac{PT_{test}}{PT_{normal}}\right)^{ISI}$$

4.**Activated Partial Thromboplastin Time** (aPTT or PTT) ⟶ measures F XII, XI, IX, VIII, X, V, II, I - (normal Time 30 – 40 secs) "intrinsic pathway"
5.**Thrombin (Clotting) Time** (TT) ⟶ sensitive to deficiency of Fibrinogen or inhibition of thrombin - (normal Time 14 – 16 secs)
6.**Bleeding Time** ⟶ (3-8 secs) (not sensitive – not specific)
-Screening tests (not sensitive to all abnormalities associated with a bleeding disorder)
-Although screening tests are used widely to identify hemostatic abnormalities associated with bleeding, they are NOT perfect
-The **Clinical suspicion** for a bleeding disorder is Critical to determine extent of the laboratory investigations

Specialized Tests

1.Mixing Study (one to one mixture of patient's plasma & known normal standard plasma, **only if PT or aPTT prolonged**)
Corrected ⟶ clotting factor deficiency (risk of bleed)
Not corrected ⟶ inhibitors or antibodies directed against the clotting factors (directed against specific factor or global inhibitors " Lupus Inhibitor, risk of thrombosis ")
2.Platelets Function Assay (PFA - 100): assess platelets function ⟶ Specificity 90 % for severe platelets dysfunction of vWD (vWF plasma levels < 25%), Sensitivity 24 – 41 % (low) in mild platelets secretion defect or Storage Pool Disease (not screening tool) Platelet function assay is not done for everyone, only after the results of mixing
3.Platelets Aggregation Tests: (5 external aggregating factors: ADP, Collagen, Ristocetin, Arachidonic Acid, Adrenaline)
4.Von Willebrand Factor (antigen & activity)
5.Factor XIII assay (FXIII Deficiency ⟶ **normal** PT & PTT)
6.Human Plasminogen Activator Inhibitor (PAI-1)
7.Alpha 2 AntiPlasmin Inhibitor (α 2 AP)

Inherited Bleeding Disorders

Hemophilia:

an **inherited** bleeding disorder caused by deficiency of coagulation factors.
(the **most common** inherited bleeding disorders)
Hemophilia is an x linked recessive disorder (الله سبحانه حمى النساء من هالمرض، لكن احيانا يجوني بالعيادة نساء فيهم هيموفيليا كيف؟ she's unlucky enough to have both xx affected (her father is affected & her mother is either a carrier or also affected). But this is extremely rare!

- **Hemophilia A** – Inherited deficiency of **factor VIII (8)**; an **X-linked** recessive disorder. Factor 8 deficiency is the most common
- **Hemophilia B** – Inherited deficiency of **factor IX (9)**; also called Christmas Disease; an **X-linked** recessive disorder.
- **Hemophilia C** – Inherited deficiency of **factor XI (11)**; also called Rosenthal Syndrome; variable pattern of inheritance but mainly an **autosomal recessive** disorder. Rarely, heterozygotes may have bleeding (ie, autosomal dominant transmission, due to heterodimer binding). especially common in Ashkenazi Jews (ie, Jews from Eastern Europe).

-Hemophilia **most likely** is congenital but sometimes can be acquired.

Hemophilia	
Congenital	Acquired
-Genetic mutation in F8 "factor 8" & F9 "factor 9" located on the long arm of **X chromosome**. -Observed commonly in **males** due to their hemizygous state (having only 1 x-chromosome) -*Rarely* in females due to (Heterozygous females as result from nonrandom X chromosome inactivation "skewed Lyonization"[5], or the presence of other genetic abnormalities (Turner Syndrome or X autosomal translocations).	Development of **autoantibodies** most commonly directed against FVIII "or F9, F11"(the factor is produced well but antibodies make it dysfunctional) – associated with pregnancy, malignancy, advanced age.

Hemophilia characterized based on the residual or **baseline factor activity level** (also referred to as "factor level"); expressed as a % of normal or in IU/mL. Hemophilia pts present with severe pain in their joint (hemarthrosis), we do a baseline factor activity level, <1 is considered severe, >40% is considered normal factor level.
Genetic mutation in factor 8 or 9.
It also can be acquired, how? Autoantibodies formed against factor 8, common in pregnancy, malignancy & unknown causes. Factor levels typically *correlate with* the degree of **bleeding Symptoms**.

Baseline factor activity level		
Severe Hemophilia	Moderate Hemophilia	Mild Hemophilia
defined as **<1 %** factor activity (<0.01 IU/mL).	defined as a factor **activity** level **≥1 %** of normal and **<5 %** of normal (≥0.01 - <0.05 IU/mL).	defined as a factor activity level **≥5 %** of normal and **<40 %** of normal (≥0.05 - <0.40 IU/mL). **Usually asymptomatic, we see them when they have undergone dental extraction or surgical procedures**

[5] Because females have 2 copies of x-chromosome, the process of x chromosome inactivation ensures that females have one functional copy of x chromosome which is the normal dosage for human. **random means that the inactivated x chromosome is randomly selected** "some women may have 35% of abnormal x chromosome, while others 65% and so on.

Clinically presents as: hematomas, **hemarthrosis**, bruising, bleeding (mucosal, GI, GU) Any type of coagulation factor deficiency may lead to **deep bleeding.**

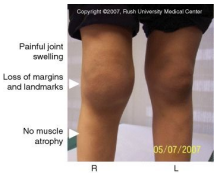
Diagnosis:

-Prolonged aPTT

-Low Factor Level (F VIII or FIX or FXI) → *the most accurate test*

-Mixing study (corrected) → *the initial test*

-Normal VWF & PT



They present with Hemarthrosis > body responds with inflammation > chronic (alternating pattern of bleeding and inflammation) > destructive arthropathy > replacement of joint

Dx as a hematologist they called you saying جانا مريض ما نعرف تشخيصه للحين، but he has severe abdominal bleeding, his ptt is 70 (double the normal) [suspect coagulation disorder], what's the 1st step to confirm factor deficiency, **mixing study!** We get the patient's abnormal plasma and the normal and mix them together, the abnormal has the prolonged ptt. When we mix them, if ptt is back to normal that means there was factor deficiency,

لان الفاكتر في البلازما الكويس صلح الخلل في البلازما الثاني، طيب واذا سويناها ومازال ٧٠ ايش المشكلة؟

acquired autoantibodies

حتى لما تحط فاكتر سليم قاعدة تضربه، فالحمدلله نقدر نعرف الانتي بوديز لفاكتر ٨،٩

so we give pt appropriate tx

Treatment: **Replacement of the deficient coagulation Factor** (recombinant or plasma derived) + Adjunctive therapy (Desmopressin (DDAVP), Antifibrinolytic agents (Tranexamic Acid, Aminocaproic Acid), recombinant FVIIa (with inhibitors).

-Treat mild cases with Desmopressin

-Severe bleeding with low factor level is treated with replacement of specific factor.

Von Willebrand disease:

-The most common bleeding disorder.

-There is either a **reduced level** or **abnormal function** of Von Willebrand factor. RIPA: Ristocetin-induced platelet aggregation

Most common inherited bleeding disorder is VWD (von willebrand disease). Dx? Ptt can be normal or prolonged based on subtype.

Classification of von Willebrand disease

Type	Inheritance	VWF activity	RIPA	Multimer pattern
Type 1 (partial quantitative deficiency)	Autosomal dominant	Decreased	Decreased	Uniform decrease; all multimers present
Type 2 (qualitative variant)				
Type 2A	Autosomal dominant or recessive	Decreased	Decreased	Decreased large multimers
Type 2B	Autosomal dominant	Decreased	Increased	Decreased large multimers
Type 2M	Autosomal dominant or recessive	Decreased	Decreased	Uniform decrease; all multimers present
Type 2N	Autosomal recessive	Normal	Normal	Normal
Type 3 (severe)	Autosomal recessive	Markedly decreased or absent	Markedly decreased or absent	Undetectable; usually cannot visualize

Von Willebrand disease	
Congenital	Acquired
-**Autosomal dominant** (most types) -Recessive (rarely, type 2M & 3)	Rare, caused by **autoantibodies** against vWF & immune complex formation, vWF binding to cancer cells, Congenital Heart Disease, Aortic Stenosis, Angiodysplasia. Rx (of the underlying disorder)

Clinically presents as:

-Typically there is **mucus membrane bleeding** (epistaxis, menorrhagia).

-Easy bruising. **Hemarthrosis and muscle hematomas are rare** (compared to hemophilia) except in **type 3.**

Diagnosis:

-**FVIII assay** (low in 2N & 3) VWF is the carrier molecule for factor 8 protecting it from premature destruction, that's why we see low level in some subtypes

-Normal aPTT in (Type 1 & 2), **prolonged aPTT** in (Type 2N, 2B, & 3) Secondary to low levels of FVIII

-**VWF:Ag** VWF antigen level is usually decreased

-VWF:RCo Ristocetin cofactor assay: defective platelets aggregation by patient plasma in the presence of ristocetin

-VWF multimers (to differentiate subtypes)

-Platelets count is normal except for type 2M **(in the book 2B not 2M)**

Test	Type 1	Type 2A	Type 2B	Type 2M	Type 2N	Type 3
VWF:Ag	↓	N or ↓	N or ↓	N or ↓	N	0
VWF:RCo	↓	↓↓↓	↓ ou ↓↓	↓↓	N	0
Agglut. high dose low dose	N or ↓ 0	↓↓↓ 0	N ++	decreased 0	N 0	0 0
F VIII	N or ↓	N or ↓	N or ↓	N or ↓	↓↓	↓↓↓
Multimers	N	IMW & HMW absent	HMW absent	N or ↓	N	0
VWF:CB	↓	↓↓	↓↓	N or ↓	N	0

Treatment:

Desmopressin (DDAVP; intranasal) "**Best initial therapy**, releases subendothelial stores of VWF"
Replacement of exogenous vWF concentrate "if there is no response to desmopressin"
Antifibrinolytic agents (Tranexamic Acid, Aminocaproic Acid),
Conjugated Estrogens & oral contraceptive Agents (for menorrhagia)

Platelets Disorders

A) Quantitative platelets disorders:

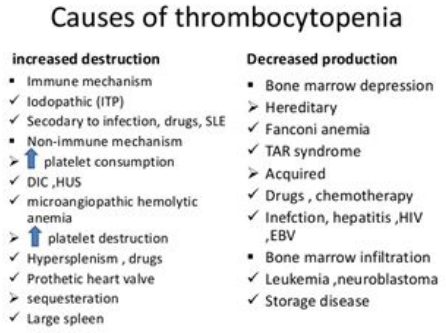
"Most common cause of bleeding → iatrogenic secondary to medications e.g. aspirin"

Thrombocytopenia:

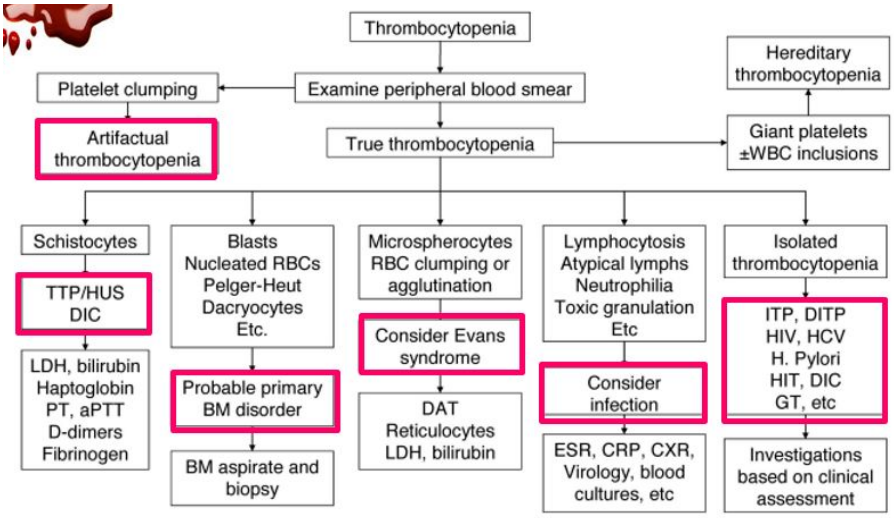
The list is long you don't have to memorize it, just go through it
Thrombocytopenia has maaaaany causes لا ممكن يجيه، لو سلمتوا عالمريض تحفظونها احنا نفسنا ماحفظناها.

- Imuran for example causes thrombocytopenia (from hx! You have to take a good one to know the cause and possible dx)
- Pseudothrombocytopenia and the drug induced one are the most common ones in people in the hospitals.

In vitro condition: احيانا بعض الناس لما نسحب منهم دم تتجمع البلاتلتس حقتهم سوا، تتخض كده وترح لامه بعضيها، فلما نحطها في المشين الغبية بتعد الخمسة بواحد فيصير العدد بدل ٢٠٠ كم؟ ٤٠! وش اسوي انا؟ اروح اقول سووها
manual counting
يروح حاطها على سلايد ويعدها وحده وحده و يرجع يقولك صارت ٢٠٠ ..
^that's "pseudothrombocytopenia"



Approach to Thrombocytopenia:



-When you do a CBC and it shows thrombocytopenia, you do peripheral blood smear and if there is platelets clumping it means that the machine counted the clumped platelets as one so that's why it showed thrombocytopenia (we call it pseudothrombocytopenia because the patient is not thrombocytopenic).
-If we have true thrombocytopenia we have variety of possibility:
1- Thrombotic thrombocytopenic purpura "hemolytic uremic syndrome" & DIC : we see schistocytes which are fragmented parts of a red blood cells as they pass through fibrin strands and they are generated by these diseases processes " TTP/HUS/DIC"
2- Blasts, nucleated RBCs typically seen with bone marrow disorders
3- Evans syndrome is a very rare autoimmune disorder in which the immune system destroys the body's red blood cells , white blood cells and/or platelets "autoimmune hemolytic anemia (AIHA)" resulting in spherocytes formation "erythrocytes that are sphere-shaped rather than biconcave disk shaped"

4-Elevated levels of lymphocytes or neutrophils indicative of underlying infection causing thrombocytopenia
5-Isolated thrombocytopenia typically seen in ITP "idiopathic thrombocytopenic purpura"
We will discuss ITP - TTP - DIC.

Immune Thrombocytopenic Purpura (ITP):

- The highest incidence has been considered to be in **women** aged 15-50 years
- The lifespan of platelets reduced to only few hours
- Increased in platelets turnover and increase in megakaryocytes number
- It is usually idiopathic but it might be secondary

Very common disorder of platelets especially in younger females if <100000 you have to consider this diagnosis! But you must consider everything else because it's a diagnosis of exclusion, so if everything else is negative this is your diagnosis.

ITP	
Primary	Secondary
Isolated thrombocytopenia "no anemia or neutropenia" due to immune mediated platelets destruction (production of autoantibodies against platelets.)	Associated with disease or drug exposure: **Viral** (HIV, HCV, HBV, EBV, CMV, Parvovirus), SLE, APLS "antiphospholipid antibody syndrome" , H. Pylori Infection, Chronic Lymphocytic Leukemia (CLL), Hodgkin Lymphoma, AIHA "autoimmune hemolytic anemia"

Clinical features: insidious onset of mucocutaneous bleed, F:M (3:1)

- Immune destruction is peripheral not central.
- Suppressed production in bone marrow
- Could be 2ndary to other causes.
- Thrombocytopenia and leukopenia and you didn't check bone marrow? Fatal mistake!
- If you give them steroids and the number is raised to 150000 now it will confirm your diagnosis because it's an immune disorder.
- Thrombocytopenia with splenomegaly? Hypersplenism (it causes thrombocytopenia more than leukopenia)

Diagnosis: Diagnosis of exclusion, no robust clinical or Lab parameters, Typically:

- CBC (**Isolated thrombocytopenia** < 100.000)
- Peripheral blood smear shows **large platelets**
- Anti-platelets antibodies (not useful)
- 10% have associated ITP + AIHA (Evans Syndrome)
- Bone marrow shows normal or increased number of megakaryocytes

Treatment:

- Rarely indicated if platelets > 50.000 unless there is bleeding, trauma/surgery, anticoagulation, comorbidities
- **Steroids**, **IVIG**, Splenectomy, if all fail >TPO agonists (Romiplostim, Eltrombopag)

Presentation	Management
No bleeding, count >30,000	No treatment
Mild bleeding, count <30,000	Glucocorticoids
Severe bleeding (GI/CNS), count <10,000	IVIG, Anti-Rho (anti-D)
Recurrent episodes, steroid dependent	Splenectomy
Splenectomy or steroids not effective	Romiplostim or eltrombopag, rituximab, azathioprine, cyclosporine, mycophenolate

Acute exacerbation:

- First: steroids!
  Don't give platelet transfusion because it will fire up the antibodies more so patients won't benefit unless they have serious bleeding حطو تحتها الفين خط you must give them platelets.
- Second: IV Ig immunoglobulin, in 2 days it will fix it all up!
  - Eg pregnant lady, platelet count 2000 tomorrow she'll give birth so what to do? Give IV Ig and tomorrow it will be 70 000 وتوكلوا على الله ولدوها
  - Steroid dose 1g per kilo, IVIG 1mg per kilo
- Forget about anti Rh!

Thrombotic thrombocytopenic purpura (TTP-HUS)

Etiology:

1. TTP is a rare disorder of platelet consumption. The cause is unknown.
2. Hyaline microthrombi (mostly platelet thrombi) occlude small vessels—any organ may be involved. They cause mechanical damage to RBCs (schistocytes on peripheral smear).
3. This is a life-threatening emergency that is responsive to therapy (see below). If untreated, death occurs within a few months.

Clinical features:

1. Hemolytic anemia (microangiopathic)
2. Thrombocytopenia
3. Acute renal failure (mild)
4. Fever
5. Fluctuating, transient neurologic signs—can range from mental status change to hemiplegia

Treatment:

1. Plasmapheresis (large volume). Begin as soon as diagnosis is established (delay in treatment is life-threatening). Response is usually good (monitor platelet count, which should increase).
2. Corticosteroids and splenectomy—may be of benefit in some cases
3. Platelet transfusions are contraindicated.

Disseminated Intravascular Coagulation (DIC)

Etiology:

- Trauma, shock, infection, malignancy (esp APML[6]), Obstetric complications. Common as well in the critically ill pt

Pathogenesis :

- **Massive activation** of coagulation that overwhelms control mechanisms → thrombosis
  Acute consumption of coagulation factors & Plts → **bleeding**
  - Ongoing thrombosis and bleeding the coagulation system went crazy!
  - Platelets نازل فيصير فاكتور الكواقيلوشن معها تاخذ، ptt and INR و نازله ينوجن والفايبر والبلاتليت الدما في ضاربة تصير الفايبرينوليتك سستم شغال

Diagnosis:

- PT and aPTT **are elevated**
- **Decreased** level of fibrinogen (may be normal because of acute phase)
- positive D-Dimer/FDP[7]
- **Decreased** level of platelets,
- positive Schistocytes
- High LDH
- Low Haptoglobin

  Diagnosis of exclusion, treat the underlying cause! You can't do anything else!

Treatment: No treatment

- Treat underlying process, FFP[8], Cryoprecipitate (Goal Fibrinogen > 100 mg/dL), Platelets concentrate

B) Qualitative platelets disorders:

Acquired Platelets Functional Disorders:

1. Liver Disease.
2. Cardiopulmonary Bypass.
3. Uremia.
4. Dysproteinemia (Multiple Myeloma or Waldenstrom Macroglobulinemia).

---

[6] Acute Promyelocytic Leukaemia
[7] fibrin degradation product
[8] Fresh frozen plasma

5. Myeloproliferative Disorders (MPDs).
6. Diabetes Mellitus.
7. Acquired Glanzmann thrombasthenia.

- Platelet normal but not functioning
- Advanced renal failure + urea can cause it
- The list is long

Inherited Disorders Of Platelets Function: Inherited→ احفظوا اثنين...وحتى الاثنين كتير عليكو

Giant platelet disorders includes Plt GP abnormalities (eg, **Bernard-Soulier Syndrome**, Deficiency of Platelet Alpha granules (eg, Gray Platelet Syndrome), Deficiency May-Hegglin Anomaly (which also involves the presence of abnormal neutrophil inclusions (ie, Döhle-like bodies)), & some kindreds with type 2B vWD (Montreal Platelets Syndrome)

1. Wiskott-Aldrich syndrome
2. Storage Pool Disorders such as Hermansky Pudlak Syndrome (HPS) (Deficiency of Dense Granules)
3. **Glanzmann thrombasthenia**
4. Platelet release disorders
5. Glycoprotein VI defects
6. Sticky platelet syndrome
7. Congenital Deficiency of the ADP receptor P2Y12
8. Scott syndrome

INHERITED DISORDERS OF PLATELETS FUNCTION الاثنين اللي يقصدها الدكتور	
Bernard-Soulier Syndrome	Glanzmann thrombasthenia
• Autosomal recessive disease • Disorder of **platelet adhesion** (to subendothelium) due to deficiency of platelet glycoprotein **GPIb-IX** • On peripheral blood smear, platelets are abnormally large. • Platelet count is <u>mildly low</u>.	• Autosomal recessive disease • Disorder of **platelet aggregation** due to deficiency in platelet glycoprotein **GPIIb-IIIa** • Bleeding time is prolonged. • Platelet count is <u>normal</u>.

- How to treat? Platelet transfusion because it's inherited, من بطل هالامراض؟ Tranexamic acid for the mucocutaneous bleeding is more effective, the visceral not as much.

_____

Drugs used for clotting disorders: (preventing formation of blood clots)

Anticoagulants			
Direct Thrombin Inhibitors	Indirect Thrombin Inhibitors	Vitamin K epoxide reductase Inhibitor	Direct Xa Inhibitors
Dabigatran Argatroban Lepirudin Bivalirudin	Unfractionated **Heparin** (UFH) LMWH - Enoxaparin LMWH - Tinzaparin LMWH - Deltaparin Fondaparinux	**Warfarin**	**Rivaroxaban** a new medication where we don't need to monitor PT and PTT and it is taken orally Apixaban Endoxaban

Antiplatelets		
Prostaglandin/COX Inhibitors	Glycoprotein IIb/IIIa Inhibitors	$P2Y_{12}$ ADP Inhibitors
Aspirin	**Abciximab** Eptifibatide Tirofiban	**Clopidogrel** Cangrelor Prasugrel Ticlopidine Ticagrelor

Thrombolytics (Plasminogen Activators)		
Tissue Plasminogen Activators(t-PA)	Streptokinase (SK)	Urokinase (UK)
Alteplase Reteplase Teneteplase	-	-

MCQs

1) 13 year old female came in with mucocutaneous bleeding and petechiae. Platelets were low at 1500, autoimmune and viral screen were negative. Rest of CBC is normal. What is the most likely diagnosis?
A. immune thrombocytopenic purpura
B. Glanzmann's disease
C. Bernard lousier
D. vWF

2) You have been called from obstetrician due to a severe bleeding after delivery. Normal PT, aPTT and platelets count and she has a brother diagnosed with bleeding disorder. What is the deficient factor?
A. factor VII
B. factor VIII
C. factor XIII

Answer key:
1 (A) | 2 (C) | 3 (A) | 4 () | 5 ()

3) 14 years old male patient presented with epistaxis and gingival bleeding, the patient denied any other bleeding, fever, lymphadenopathy. The platelet count was 9000 he had severe thrombocytopenia, peripheral Smear showed no evidence of ruptured or abnormal blood cells. LDH level was 153 (normal). What is the best management in this case?
A. Fresh frozen plasma
B. Plasmapheresis

Summary of lab findings:

TABLE 9-5 Laboratory Findings for Bleeding Disorders

Condition	Platelet Count	Bleeding Time	PT	PTT
Hemophilia	NL[a]	NL	NL	Increased
vWD	NL	Increased	NL	Increased
ITP	Decreased	Increased	NL	NL
TTP	Decreased	Increased	NL	NL
DIC	Decreased	Increased	Increased	Increased
Heparin	NL or decreased	NL	NL	Increased
Warfarin	NL	NL	Increased	NL
Liver disease	NL	NL	Increased	Increased

[a]NL = normal.