Bleeding Disorders

Objectives:

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

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Revised By:

Resources: 435 team + Davidson + kumar + Recall questions step up to medicine.

- Editing file
- Feedback

Hemostasis

★ Definition:

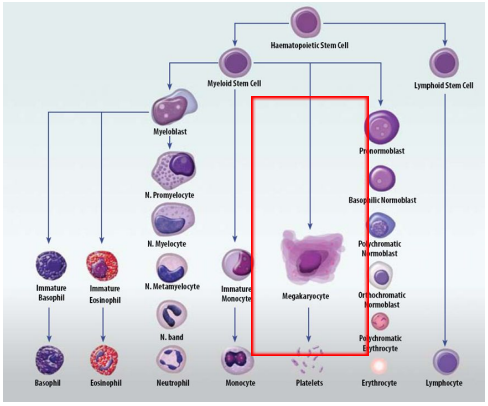
The process through which bleeding is controlled at a site of damaged or disrupted endothelium.

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).

★ Platelets: main function is primary homeostasis



- 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 & kidney)
- Normal platelets counts (150 – 400 x 10^9)
- Platelets life span (**7 – 10 days**)

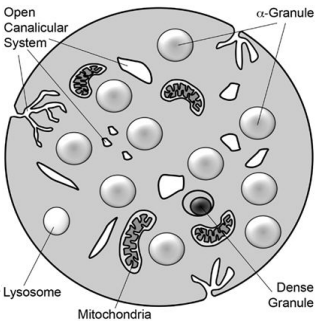
Platelets ultrastructure: Extremely small & discoid (3 x 0.5 µm in diameter)

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** and collagen
- 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)



[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 platele

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)

- release of α granules contents, & ADP from dense granules
- Formation of Thromboxane A2 by various agonists induces intracellular signaling.

★ 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: secondary homeostasis

★ 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.

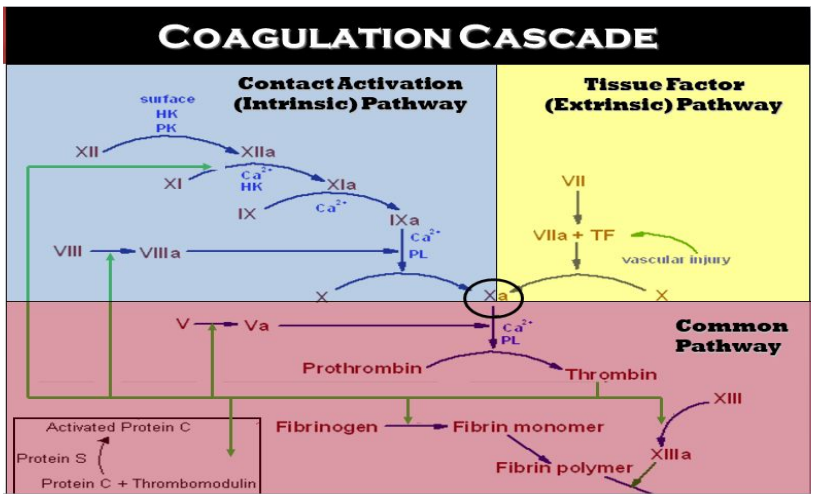
★ Extrinsic pathway:

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).

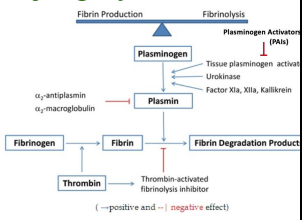
- Extrinsic pathway is what gets activated in times of injury. but its activation is not sufficient and we need the intrinsic pathway but how the intrinsic pathway gets activated? when factor 7 activates factor 10 and factor 10 activates prothrombin to thrombin, thrombin will activate intrinsic pathway (thrombin activates factor 5,7,8,11,13).
- 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'.**
- At the end of this phase (coagulation cascade) fibrinolysis phase follows. the end product of fibrinolytic system is D-dimer. high d-dimer levels means there is a thrombus somewhere in the body and is being destroyed.

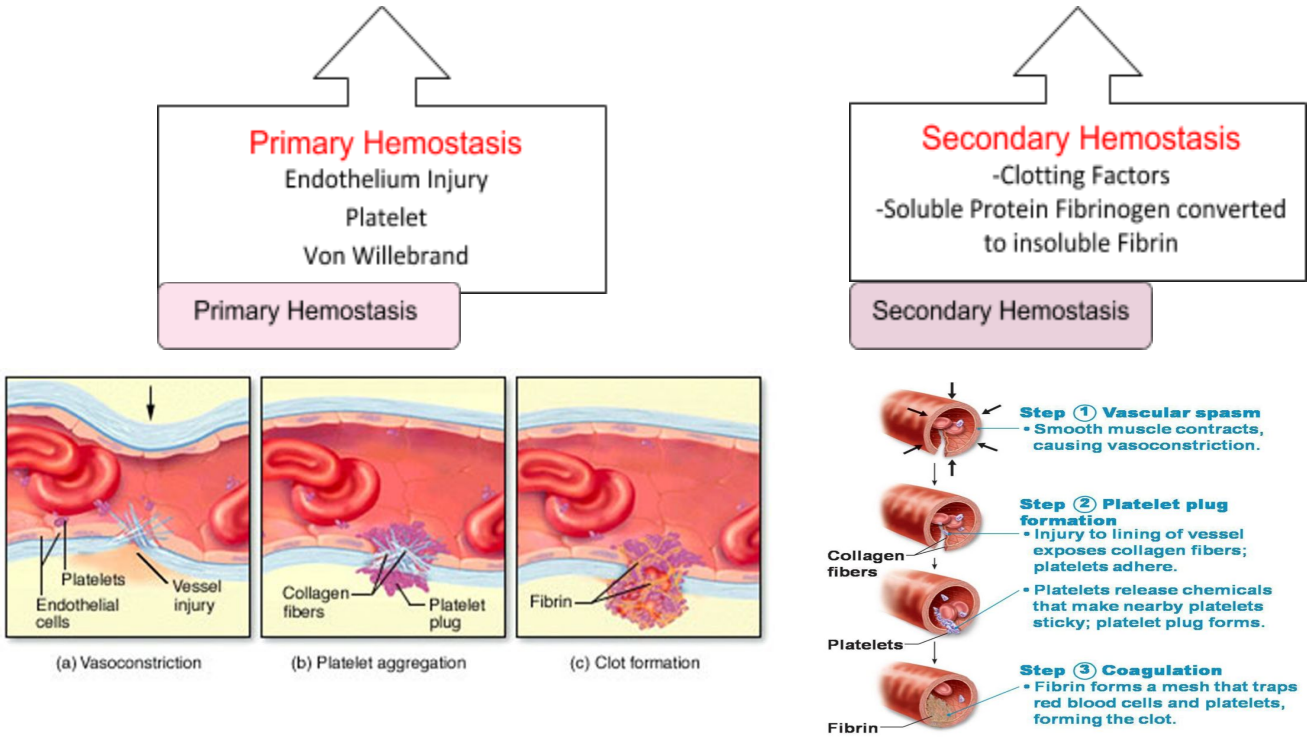


Clotting Factors in Blood and Their Synonyms

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	

★ 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 to reduces blood flow.	• Platelets Adhesion & Aggregation (via VWF, Gp Ib, Gp IIa, ADP, TXA2). • Formation of **Platelet Plug**. • Fragile and not enough to stop the bleeding.	• 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. plasminogen is the major player. 



- The main function of the **primary hemostasis** is to form Platelet plug
- The main function of the **secondary hemostasis** is to form fibrin clot

Congenital or Inherited Bleeding Disorders

★ Hemophilia:

an **inherited** bleeding disorder caused by deficiency of coagulation factors.

- **Hemophilia A** – Inherited deficiency of **factor VIII (8)**; an **X-linked** recessive disorder. can only affect male and rarely females if the mother has affected X and the father has the disease.
- **Hemophilia B** – Inherited deficiency of **factor IX (9)**; also called Christmas Disease; an **X-linked** recessive disorder. less common than A.
- **Hemophilia C** – very rare, 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 FIX (the factor is produced well but antibodies make it dysfunctional) – associated with pregnancy, malignancy (lymphoma, chronic lymphocytic leukemia), 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.
Factor levels typically *correlate with* the degree of **bleeding Symptoms**.

[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.

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).

with severe Hemophilia should be treated with regular transfusion to prevent any serious bleed.

★ **Clinically presents as: secondary hemostasis (Coagulopathy):** hematomas, **hemarthrosis**, bruising, petechial rash يقع زرقاء, bleeding (mucosal, GI, GU, CNS, JOINT) **deep bleeding.**

★ Diagnosis:

- **Prolonged aPTT** intrinsic pathway
  - **Low Factor Level (F VIII or FIX or FXI) → *the most accurate test***
  - **Mixing study (corrected) → *the initial test***
  - **Normal VWF & PT**

★ **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. leave without treatment unless they bleed we replace factors.
- Severe bleeding with low factor level is treated with replacement of specific factor. regular lifetime factor replacement 2 to 3 times a week.
- moderate according to situation: frequent bleed → maintenance factor replacement, otherwise will give factors upon bleeding.

★ Von Willebrand disease:

- The most common bleeding disorder.
- There is either a **reduced level** or **abnormal function** of Von Willebrand factor. not required to know all types.

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 in some other conditions • 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. lymphoma. CLL. Infection. 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)
- Normal aPTT in (Type 1 & 2), **prolonged aPTT** in (Type 2N, 2B, & 3)
- **VWF:Ag**
- VWF:RCo
- VWF multimers (to differentiate subtypes)
- Platelets count is normal except for type 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** in mild cases which stimulates endogenous production of VWF,
Replacement of exogenous vWF concentrate,
Antifibrinolytic agents (Tranexamic Acid, Aminocaproic Acid) givin for all bleeding patients and contraindicated in thrombosis,
Conjugated Estrogens & oral contraceptive Agents (for menorrhagia).

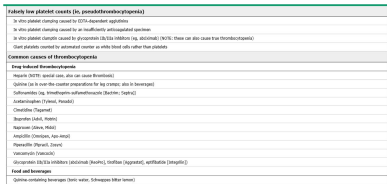
Platelets Disorders

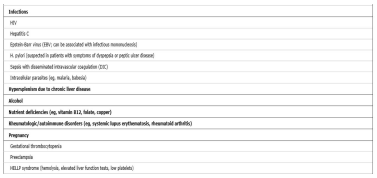
Quantitative platelets disorders:

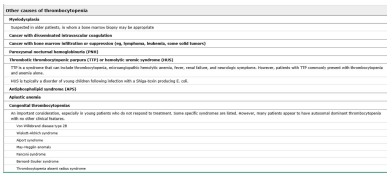
★ Thrombocytopenia:

Causes of thrombocytopenia:

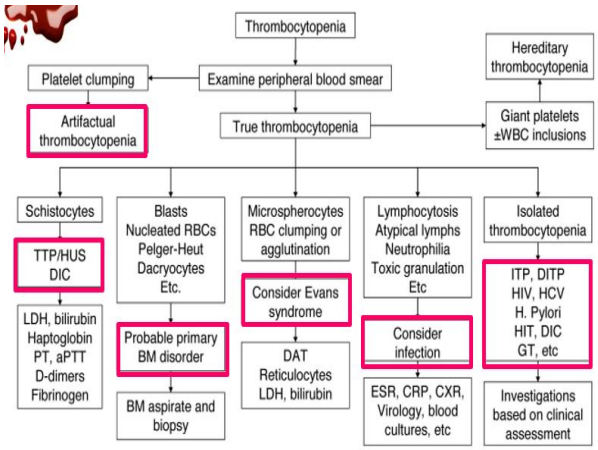
almost everything causes thrombocytopenia don't memorize all causes. most common cause in hospitalized patients is drug induced thrombocytopenia (chemotherapy) and pseudothrombocytopenia which is blood clumping in vitro and you need to first roll it out.



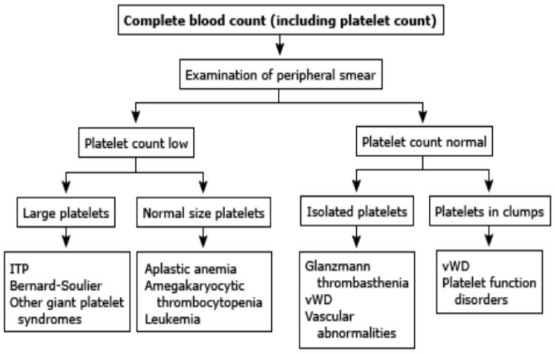




★ Approach to thrombocytopenia:



Diagnostic approach to a patient with mucocutaneous bleeding (purpuric disorders)



thrombocytopenia: less than 150,000 → you order peripheral blood smear and manual platelet count. Giant platelet → most probable cause is hereditary thrombocytopenia, Schistocytes → TTP top emergency in hematology because high mortality within 24 hours, >20% blast → leukemia, microspherocytes and RBCs clumping or agglutination → Evans syndrome you do reticulocyte count + ldh + bilirubin, lymphocytosis + atypical lymphs and neutrophils toxic granules → infection, isolated thrombocytopenia → ITP or viral infection.

- blood smear critical in approaching thrombocytopenia
- mixing study critical in approaching coagulopathy and DIC

★ Immune Thrombocytopenic Purpura (ITP): very common

ITP	
Primary	Secondary
Isolated thrombocytopenia due to immune mediated platelets destruction (production of autoantibodies against platelets.) diagnosis of exclusion.	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 evans syndrome"

★ Clinical features: insidious onset of mucocutaneous bleed, F:M (3:1). deep tissue bleeding and hemarthrosis.

★ Diagnosis:

Unless platelet isn't less than 10.000 treatment is not required.
No cut off but if treated for other reasons stop above 40.000 (put it in context with treatment below)
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).

★ Treatment:

- Rarely indicated if platelets > 50.000 unless there is bleeding, trauma/surgery, anticoagulation, comorbidities.
- **Steroids**, **IVIG**, Splenectomy, TPO agonists (Romiplostim, Eltrombopag). Steroids is first line treatment (0.5-2 mg/kg daily), if no response stop steroids and give IVIG (1gm/kg daily), not responding splenectomy, not responding thrombopoietin agonists.

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

★ Disseminated Intravascular Coagulation (DIC): common in clinically ill patients.

★ Etiology:

- Trauma, shock, infection (septic shock), malignancy (esp APML[6]), Obstetric complications (preeclampsia and IUFD).

★ Pathogenesis:

- **Massive activation** of coagulation that overwhelms control mechanisms → thrombosis
  Acute consumption of coagulation factors & Plts → **bleeding.**

★ 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

★ Treatment:

- Treat underlying process, FFP[8] don't give FFP and Factors if the patient is not bleeding, Cryoprecipitate (Goal Fibrinogen > 100 mg/dL), Platelets concentrate

★ Thrombotic Thrombocytopenic Purpura/ Hemolytic Uremic Syndrome (TTP/HUS):

★ Etiology and Pathogenesis:

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

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

Primary: isolated thrombocytopenia due to immune Plt destruction & production of (auto AB to megakaryocytes)

Secondary: a/w disease/drug exposure, Viral (HIV, HCV, HBV, EBV, CMV, Parvovirus), SLE, APLS, H. Pylori Infection, Chronic Lymphocytic Leukemia (CLL), Hodgkin Lymphoma, AIHA

★ Diagnosis:

Dx of exclusion, no robust clinical or Lab parameters, Typically CBC (Isolated MPLT < 100.000), 10% have ITP + AIHA (Evans Syndrome), PBS (Large Plts), Anti-PltAB (not useful).

★ Clinically:

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

- Hemolytic anemia (microangiopathic)
- Thrombocytopenia
- Acute renal failure (mild)
- Fever
- Fluctuating, transient neurologic signs—can range from mental status change to hemiplegia

★ Treatment:

rarely indicated if PLT > 50.000 unless bleeding, trauma/surgery, anticoag, comorbidities Steroids, IVIG, Splenectomy, TPO agonists (Romiplostim, Eltrombopag)

- 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).
- Corticosteroids and splenectomy—may be of benefit in some cases
- Platelet transfusions are contraindicated.

Qualitative (Functional) platelets disorders:

functional level means platelet count is normal but function is distorted famous example is uremia patients → do platelet function assay.

★ Acquired Platelets Functional Disorders:

- Liver Disease.
- Cardiopulmonary Bypass.
- Uremia.
- Dysproteinemia (Multiple Myeloma or Waldenstrom Macroglobulinemia).
- Myeloproliferative Disorders (MPDs).
- Diabetes Mellitus.
- Acquired Glanzmann thrombasthenia.

★ Inherited Disorders Of Platelets Function:

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).

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

INHERITED DISORDERS OF PLATELETS FUNCTION rare	
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 mildly low.	• Autosomal recessive disease • Disorder of **platelet aggregation** due to deficiency in platelet glycoprotein **GPIIb-IIIa** • Bleeding time is prolonged. • Platelet count is normal.

Approach to Patient with Potential Bleeding

★ 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).

★ Laboratory Testing:

★ Screening Tests:

- **CBC** (Platelet count).
- **Prothrombin Time (PT)** → measures **FVII, X, V, II, I** - (normal time 10-14 secs) "extrinsic pathway".
- **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.

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

- **Activated Partial Thromboplastin Time** (aPTT or PTT) → measures F XII, XI, IX, VIII, X, V, II, I - (normal Time 30 – 40 secs) "intrinsic pathway".
- **Thrombin (Clotting) Time** (TT) → sensitive to deficiency of Fibrinogen or inhibition of thrombin - (normal Time 14 – 16 secs).
- **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

- **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 (directed against specific factor or global inhibitors "Lupus Inhibitor, risk of thrombosis").
- **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).

- **Platelets Aggregation Tests:** (5 external aggregating factors: ADP, Collagen, Ristocetin, Arachidonic Acid, Adrenaline).
- **Von Willebrand Factor** (antigen & activity).
- **Factor XIII assay** (FXIII Deficiency → **normal** PT & PTT).
- **Human Plasminogen Activator Inhibitor** (PAI-1).
- **Alpha 2 AntiPlasmin Inhibitor** (α2 AP).

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

Anticoagulants secondary hemostasis disorders			
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** indicated for venous thrombosis. most used in hospitals.	**Rivaroxaban** a new medication where we don't need to monitor PT and PTT and it is taken orally Apixaban Endoxaban

Antiplatelets primary hemostasis disorders		
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	-	-

★ Management in the Perioperative Stage: go through them quickly.

★ Management of Bleeding Patient:

- Therapeutic decisions should not be based solely on laboratory testing, since abnormalities in Plt function as measured by the tests mentioned are not necessarily predictive of the presence or absence of clinical bleeding.
- Since medications such as ASA are the most common causes of Plt dysfunction, a **careful history of medication use**, including use of over-the-counter aspirin-containing preparations, is crucial >> the most prudent decision prior to an operation or other invasive procedure may simply be to **withhold any medication in question prior to the procedure.**
- If a pt has a Hx of clinically significant bleeding suggestive of Plt dysfunction, whether provoked or spontaneous, **appropriate Plt function tests should be obtained** so that risk for bleeding can be adequately assessed and therapy chosen more rational.
- **Desmopressin (dDAVP)** is commonly used to correct the hemostatic defect in VWD (releases endogenous VWF from the endothelium) - effective in preventing bleeding after dental extraction and minor surgery in pts with milder Plt defects, including storage pool disease, acquired platelet dysfunction, cirrhosis or uremia, & cardiopulmonary bypass. **significantly** reduced mean operative and early postoperative blood loss. Plasma levels of vWF were higher after desmopressin than placebo.
- **Platelet transfusion >>** may be required in pts with disordered Plt function - indicated in cases of severe, uncontrolled bleeding, when prior treatments (eg, dDAVP, estrogen) have been unsuccessful, and/or in the presence of, or anticipation of, excessive traumatic or surgical bleeding.
- **Antifibrinolytic Agents (Tranexamic Acid, epsilon Aminocaproic Acid) >>**may be helpful in reducing bleeding in pts with disordered plt function following dental extraction.
- **Conjugated Estrogens >>** used most commonly for uremic bleeding or in pts with mild to moderate type 1 vWD. Intravenous estrogen 0.6 mg/kg per day for 4-5 days, oral estrogen 50 mg/kg per day, or transdermal estradiol 50 to 100 mcg/24 hours applied as a patch twice weekly have been shown to be effective, particularly for GI bleeding.
- **Erythropoietin >>** used successfully in uremic pts to both reduce and prevent bleeding
- **Recombinant Factor VIIa (rFVIIa)>>**some success for Rx of bleeding in pts with congenital Plt disorders. Potential mechanisms >> a local procoagulant effect at sites of vascular damage or tissue factor-independent thrombin generation induced by binding of rFVIIa to the surface of activated Plts. Pts who cannot receive platelet transfusions because of alloimmunization or antibody formation to the absent platelet glycoprotein (eg, Glanzmann Thrombasthenia and Bernard-Soulier Syndrome) may benefit from rFVIIa. one or more bolus infusions of approximately 90 to 100 mcg/kg. approved in Europe for use in pts with Glanzmann thrombasthenia refractory to Plt Tx. Benefits of rFVIIa must be balanced against the risk of thrombosis.

★ Preoperative management of agents affecting homeostasis:

Warfarin:

- typically discontinue 5 days before elective surgery (ie, last dose of warfarin is given on day minus 6).
- check the PT/INR on the day before surgery & If INR is >1.5 >> ?? administer low dose oral vitamin K (1 - 2 mg) to hasten normalization of the PT/INR and recheck the following day.
- proceed with surgery when the INR is ≤ 1.4 (An INR in the normal range is especially important in ptsundergoing surgery asswith a high bleeding risk (eg, intracranial, spinal, urologic) or if neuraxial anesthesia is to be used). if bleeded give iv vit K

- Heparin / LMWH Bridging considered >> Pts with very high or high thromboembolic risk.

Name or class of drug	Clinical considerations	Recommended strategy for surgery with brief NPO state	Recommended strategy for surgery with prolonged NPO state
Aspirin	Continuation may cause perioperative hemorrhage. Discontinuation may increase the risk of vascular complications. **Discussion with cardiologist appropriate for patients with cardiovascular indications.**	Discontinue aspirin approximately 7 days prior to noncardiovascular surgery.	Resume with oral intake.
P2Y12 receptor blockers (clopidogrel, prasugrel, ticlopidine, ticagrelor)	When used after cardiac stenting procedure, if discontinued can cause cardiac ischemia perioperatively. If continued can result in bleeding complications. Should discuss management with cardiologist.	Ideally, elective procedures should be delayed until the mandatory period of platelet inhibition with these agents is completed. When used for long-term stroke prophylaxis, should be discontinued 7 to 10 days. If discontinuing, stop clopidogrel and ticagrelor at least 5 days, prasugrel 7 days, and ticlopidine 10 days before surgery. When restarting clopidogrel, consider using a loading dose.	Resume with oral intake.

Perioperative management of oral direct thrombin inhibitors and factor Xa inhibitors

Anticoagulant	Renal function and dose	Interval between last dose and procedure NOTE: No anticoagulant is administered the day of the procedure		Resumption after procedure	
		High bleeding risk	Low bleeding risk	High bleeding risk	Low bleeding risk
Dabigatran	CrCl >50 mL/minute Dose 150 mg twice daily	Give last dose three days before procedure (ie, skip four doses on the two days before the procedure)	Give last dose two days before procedure (ie, skip two doses on the day before the procedure)	Resume 48 to 72 hours after surgery (ie, postoperative day 2 to 3)	Resume 24 hours after surgery (ie, postoperative day 1)
	CrCl 30 to 50 mL/minute Dose 150 mg twice daily	Give last dose five days before procedure (ie, skip eight doses on the four days before the procedure)	Give last dose three days before procedure (ie, skip four doses on the two days before the procedure)		
Rivaroxaban	CrCl >50 mL/minute Dose 20 mg once daily	Give last dose three days before procedure (ie, skip two doses on the two days before the procedure)	Give last dose two days before procedure (ie, skip one dose on the day before the procedure)		
	CrCl 30 to 50 mL/minute Dose 15 mg once daily				
Apixaban	CrCl >50 mL/minute Dose 5 mg twice daily	Give last dose three days before procedure (ie, skip four doses on the two days before the procedure)	Give last dose two days before procedure (ie, skip two doses on the day before the procedure)		
	CrCl 30 to 50 mL/minute Dose 2.5 mg twice daily				
Edoxaban	CrCl 50 to 95 mL/minute Dose 60 mg once daily	Give the last dose three days before the procedure (ie, skip two doses on the two days before the procedure)	Give the last dose two days before the procedure (ie, skip one dose on the day before the procedure)		
	CrCl 15 to 50 mL/min Dose 30 mg once daily				

★ Preoperative Heparin Bridging:

generally initiate heparin bridging 3 days before a planned procedure (2 days after stopping warfarin), when the PT/INR has started to drop below therapeutic range.

PRE OP.

- **LMWH >>** discontinue 24 hours before the planned surgery or procedure, based on a biologic half-life of most subcutaneous LMWH of ~3-5 hours. If a twice-daily LMWH regimen is given >> evening dose the night before surgery omitted. if a once-daily regimen is given (Dalteparin 200 IUs/kg), ½ of the total daily dose is given on the morning of the day before surgery >> ensures that no significant residual anticoagulant will be present at the time of surgery.
- **UFH >>** Therapeutic dose IV infusion continue until 4-5 hours before the procedure, based on the biologic half-life of IV UFH of ~45 minutes. If SC UFH is used (dose of ~ 250 IUs/kg BID), the last dose can be given the evening before the procedure.

POST OP Resumption of UFH & LMWH is similar, based on the onset of anticoagulation at ~ 1 hour after administration for both forms of heparin (peak anticoagulant activity at ~ 3-5 hours)

- The resumption of bridging, especially when given as a therapeutic-dose regimen >> should be delayed until there is adequate hemostasis based on a clinical assessment of the wound site, drainage fluid amount, and expected postoperative bleeding; coupled, where appropriate, with hemoglobin levels >> This assessment will vary depending on the surgery type and individual pt considerations, and it may be difficult for surgery where ongoing bleeding is not readily apparent (eg, cardiac, intracranial).
- **For Major Surgery** or those with a high bleeding risk procedure >> therapeutic-dose UFH or LMWH should be **delayed for 48 to 72 hours after hemostasis** has been secured.
- **For Minor Procedures** associated with a low bleeding risk in which bridging is used (eg, laparoscopic hernia repair) >> therapeutic-dose UFH or LMWH can usually be **resumed 24 hours after the procedure.**

★ Coagulation Factor Levels Required For Hemostasis:

Factor	Plasma half-life	Hemostatic level*
Fibrinogen	2 to 4 days	50 to 100 mg/dL
Prothrombin (factor II)	3 to 4 days	20 to 30 percent
Factor V	36 hours	15 to 20 percent
Factor VII	4 to 6 hours	15 to 20 percent
Factor X	40 to 60 hours	15 to 20 percent
Factor XI	40 to 70 hours	15 to 20 percent
Factor XIII	11 to 14 days	2 to 5 percent
Factor V + factor VIII combined deficiency	36 hours for factor V and 10 to 14 hours for factor VIII	15 to 20¶ percent
Multiple vitamin K-dependent factor deficiencies (factors II, VII, IX, X)	Refer to individual factor half-lives above	15 to 20¶ percent

★ Inhibitors:

1. Antithrombin III	A serin protease inhibitor (serpin) that degrades the serine proteases; (thrombin, IXa, Xa, XIa, XIIa). Constantly active, but its adhesion to these factors is increased by the administration of heparin. Quantitative or qualitative deficiency of antithrombin (in born or acquired) leads to Thrombophilia.
2. Protein C & Protein S	Activated to PCa by thrombin bound to thrombomodulin (protein on the surface of endothelial cells); then degrades (VIIIa & Va), reducing further thrombin generation. PS acts as cofactor of PC by enhancing binding of PCa to phospholipid surface; both contain gal residues.
3. Tissue Factor Pathway Inhibitor (TFPI)	Inhibits VIIa-related activation of IX & X after its original initiation.

Summary

Coagulation Disorders

- **Visceral bleeding**: Intraabdominal, intracerebral , joints , muscles
- **Bruises**
- **Diagnostic test: coagulation profile + mixing study**

	Hemophilia A & B		Von willebrand disease	
Etiology	**Inherited**	**Acquired**	**Inherited**	**Acquired**
Diagnosis	▪ **Prolonged PTT** ▪ Normal VWF & PT		▪ **Prolonged PTT** ▪ **Factor 13 assay** ▪ **VWF antigen level**	
	Mixing study: CORRECTED PTT	**Mixing study:** Still prolonged PTT		
Treatment	▪ Coagulation factors replacement ▪ **Tranexamic acid**	▪ **Bypassing agent**	**Replacement** of exogenous VWF	

Platelet Disorders

- **Mucocutaneous bleeding - Petechial rash – Epistaxis - Menorrhagia**
- **Diagnostic test: peripheral blood smear usually**

Quantitative	Drug-related	DIC	TTP	ITP
Features:	most common	**Critically ill / ICU patients** ▪ **Septic shock** ▪ Major trauma · Coagulation profile **ABNORMAL:** ▪ **high PTT.PT.INR, D-dimer, LDH,** ▪ **Low fibrinogen, haptoglopin, Thrombocytopenia**	**Remember the 5 features of TTP :** 1. **Fever** 2. **Angiopathic hemolytic anemia** 3. **Thrombocytopenia** 4. **Renal failure** 5. **Neurological deficit** ▪ **Thrombocytopenia** · Coagulation profile **NORMAL** ▪ **Positive +ve schistocytes**	▪ Young female · **Primary:** ISOLATED thrombocytopenia ▪ autoantibodies destruction due to unknown cause · Start investigations when the platelets are **<100,000** · **Secondary** to another disease

		▪ **Positive +ve schistocytes** ▪ Can go into bleeding and or thrombosis		
Treatment	Stop the drug	**Treat the underlying cause** + **observe**	▪ **Plasmapheresis** ▪ Platelets transfusion is CONTRAINDICATED	▪ **No bleeding**, count >50,000: **NO treatment** ▪ **First line:** glucocorticoids ▪ **Second:** IVIG ▪ **Third:** splenomegaly or TPO agonist
Qualitative	**Secondary to another disease**		**Bernard soulier**	**Glanzmann thrombasthenia**
Features:	**Uremia (Renal disease)**		**GPIb-IX deficiency**	**GPIIb-IIIA**

Questions

1. Haemophilia B is a reduction in:?

A. Factor IX and so affects the intrinsic pathway

B. Factor XI and so affects the extrinsic pathway

C. Factor IX and so affects the extrinsic pathway

D. Factor VIII and so affects the intrinsic pathway

2. Which of these characteristics is more likely to be found in a coagulation defect, as oppose to a platelet defect?

A. Retro-peritoneal bleeding

B. Petechiae

C. Superficial bruises

D. Non-recurrent prolonged bleeding

3. A defect in which of these coagulation factors would result in abnormal PT and PTT?

A. Factor VII

B. Factor II

C. Factor XII

D. Factor IX

4. An isolated, prolonged partial thromboplastin time (PTT) may be due to all of the following conditions EXCEPT:

A. Heparin therapy

B. Disseminated intravascular coagulopathy

C. Lupus anticoagulant

D. von Willebrand's disease

E. Factor IX deficiency

4. Which of the following statements regarding disseminated intravascular coagulation (DIC) is TRUE:

A. Thrombosis is more common than bleeding

B. There is an increase in factor VIII levels

C. It may result from endothelial cell injury

D. The prothrombin time (PT) is normal

E. The fibrinogen is increased

Answers:

1. A

2. A

3. B

4. B

5. C

الحمدلله على التمام، والشكر له على جزيل العطاء والامتنان، ونسأله الرفعة في العلم والعمل، فمنه التوفيق وله الابتهال.
خالص الشكر والتقدير لجميع أعضاء وقادة فريق طب الباطنة على جهودهم، فلولا الله ثم هم لما كان ماكان من خالص العمل وجميل العطاء، كما ونسأل الله أن يكون فيما قدمنا النفع لكم في حاضركم ومستقبلكم بما نهلتم به من علم، والنفع لنا بالأجر والمثوبة.
تمنياتنا لكم بغدٍ مجدّ ومستقبلٍ مشرق.

- مع تحيات فريق طب الباطنة.