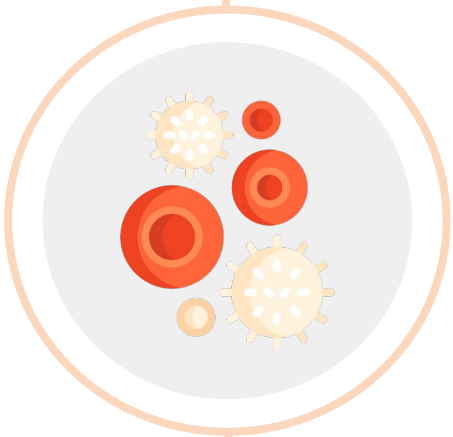
Bleeding Disorders



Objectives :

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

Editing file

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Overview

Bleeding disorder

Bleeding disorders are a group of disorders that share the **inability to form a proper blood clot.** They are characterized by **extended bleeding after injury, surgery, trauma or menstruation.**

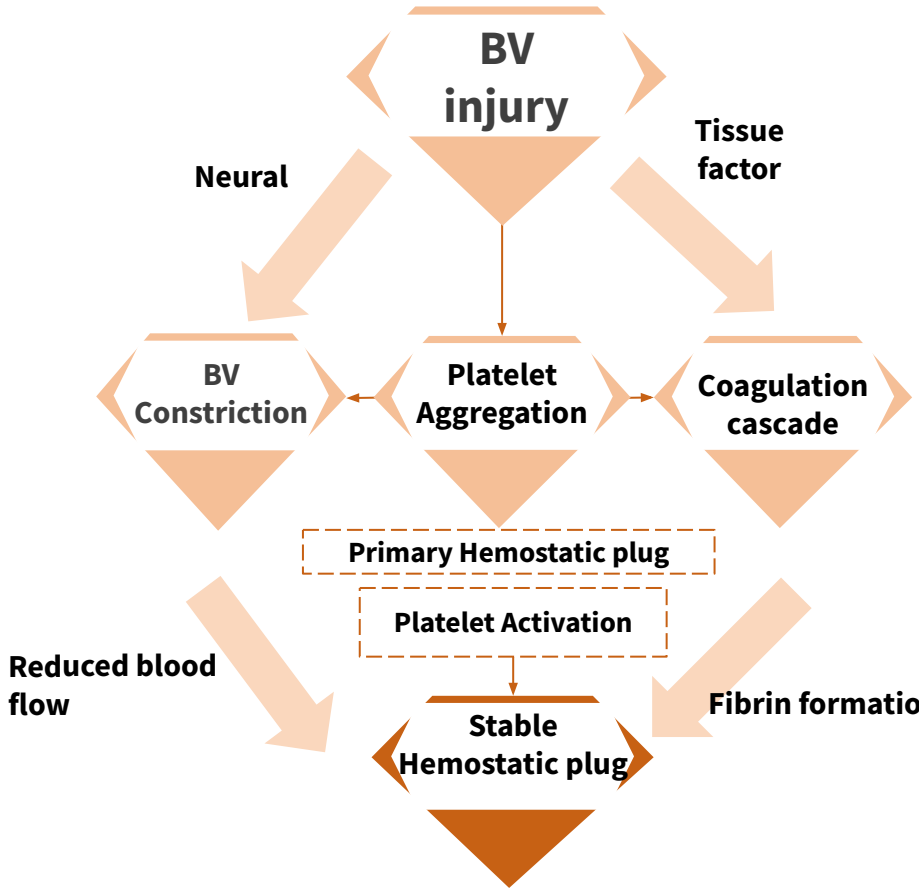
Hemostasis

- The process through which bleeding is controlled at a site of damaged or disrupted endothelium.
- A dynamic interplay between:

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

Recall the normal hemostatic process which comprises 4 main steps :

- ❑ Injury of blood vessels and rapid vasoconstriction.
- ❑ Temporary platelet plug.
- ❑ Blood coagulation by activation of the clotting cascade.
- ❑ Fibrinolytic system activation (clot dissolve by plasmin).



Lab test [2]

- **CBC to look for the Plt.**
- **Bleeding time,(CT).**
- **PT.**
- **PTT.**

Plt Study

- **Morphology.**
- **Function.**
- **Antibody.**

1- It is a natural process in our body to stop further thrombosis events . If the patient has tendency for thrombosis, anticoagulation might be needed.

2- To assess the hemostatic system if it works probably .

Platelets

◀ Platelet:

- Produced in the Bone Marrow by fragmentation of the cytoplasm of megakaryocytes.
- Each megakaryocytes rise Plt from **1000 to 5000**.
- Time interval from differentiation of the human stem cell to the production of Plts **(~10 days)** (MCQ)
- Thrombopoietin is the major regulator of Plt production via c-MPL receptor (produced by the liver & kidney).
- **Normal PLT counts (150 – 400 x 10^9).** (Usually we can do surgeries if plt count was <30, except CNS surgeries, it has to be >100k.)
- **PLT Life Span (7 – 10 days).** MCQ

◀ Platelet ultrastructure :

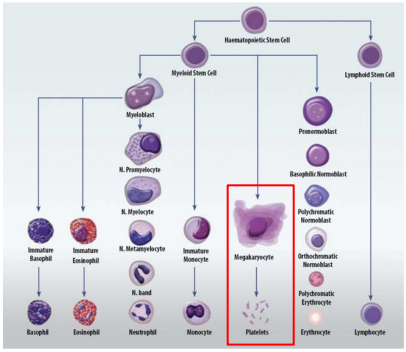
★ Extremely small & discoid (3 x 0.5 µm in diameter).

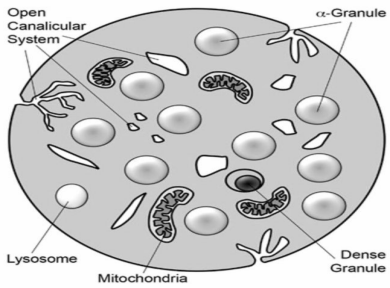
3 types of storage granules

α Granules
1. Clotting Factors[1]
2. **VWF**
3. PDGF
4. ILGF1

Dense Granules (δ)
1. **ADP** & ATP[2]
2. Serotonin
3. Histamine
4. Ionized Ca[3]

Lysosomes
1. Hydrolyticenzymes.





◀ PLTs functions :

Deficiencies in any of them produce a different disease

1- Adhesion

Adhesion between the **PLT and the vessel wall by VWF through GP Ib/IX/V** (synthesized in endothelial cells & megakaryocytes / stored in storage granules of endothelial cells & α granules of Plt / Rise with stress, exercise, adrenaline, infusion of DDAVP). DDAVP is Desmopressin. It has many uses and one of them is in vWF deficiency.

2- Aggregation

By cross linking of **PLT to PLT by VWF & Fibrinogen through GP IIb/IIIa receptors** (on the surface of the PLT).

3- Release Reaction & Amplification (aggregation formation & stabilization)

- Release of α granules contents, & ADP from dense granules.
- Formation of **Thromboxane A2** (through COX enzymes. Aspirin works by inhibiting COX enzyme thus decreasing TXA2 production) by various agonists induces intracellular signaling & thrombin formation

◀ PLTs Inhibitors:

- The goal is just to stop the bleeding. We don't want extra aggregation
- These mechanisms can be impaired in conditions that affect the endothelium, such as APS and vasculitis.

Prostacyclin (PGI2);

- Synthesized by vascular endothelial cells. Think of it as a TXA2 antagonist.
- **Potent inhibitor of PLT aggregation** & causes mild vasodilation by rising cAMP.
- Prevents Plt deposition on normal vascular endothelium

Nitric Oxide (NO);

- Released from endothelial cells, macrophages, & platelets.
- Inhibits Plt activation & **promotes vasodilation.**

1- in the platelets, different than those synthesized in the liver
2- They provide the energy for the platelets to aggregate together in the fibrin.
3- essential co-factor in coagulation cascade. hypocalcemic patients sometimes get purpuric eruptions.

Hemostasis

◀ Hemostasis dependent upon :

- Vessel Wall Integrity .
- Adequate Numbers of Platelets.
- Proper Functioning Platelets.
- Adequate Levels of Clotting Factors .
- Proper Function of Fibrinolytic Pathway.

◀ Hemostatic phases : (MCQ)

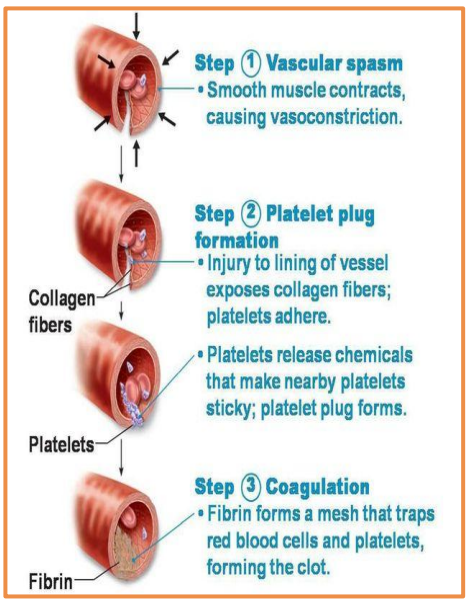
- **Primary Hemostasis:**
  1. Endothelium Injury
  2. Platelet plug
  3. Von Willebrand Factor
- **Secondary Hemostasis**
  1. Clotting Factors
  2. Soluble Protein Fibrinogen converted to insoluble Fibrin.

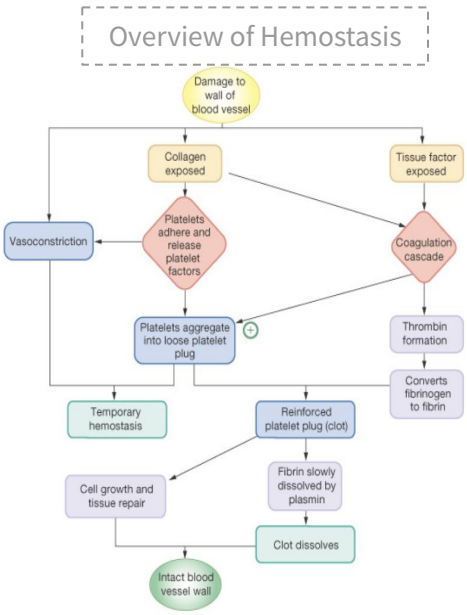
01 **Vascular phase :**
release of locally active vasoactive agents (Endothelin, Thromboxane A2, Fibrinopeptides) lead to **vasoconstriction** at the site of injury that leads to reduced blood flow.

02 **Platelet phase:**
Plt Adhesion & Aggregation (via VWF, ADP, TXA2) will result in formation of **PLT Plug**.

03 **Plasma coagulation phase:**
Propagation of the clotting process by the coagulation cascade lead to formation of **Fibrin Clot**.

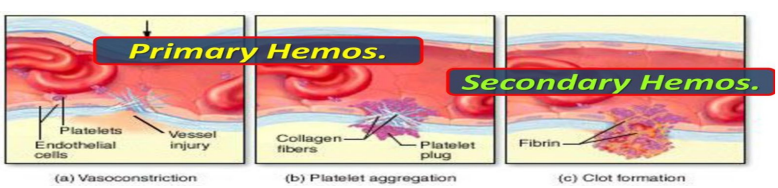
04 **Fibrinolysis change :**
Termination of clotting by antithrombotic control mechanisms & **removal of the clot.**





Primary VS secondary hemostasis
Primary hemostasis refers to platelet aggregation and platelet plug formation. Secondary hemostasis refers to the deposition of insoluble fibrin, which is generated by the proteolytic coagulation cascade. This insoluble fibrin forms a mesh that is incorporated into and around the platelet plug.

- Defect in 1ry → Mucosal bleeding; normal PT/PTT
- Defect in 2ndry → Deep tissue bleeding; abnormal PT/PTT, depending of the pathway affected:
  - **Intrinsic pathway → prolonged PTT**
  - **Extrinsic pathway → prolonged PT**
  - If both are prolonged think of DIC



Hemostasis

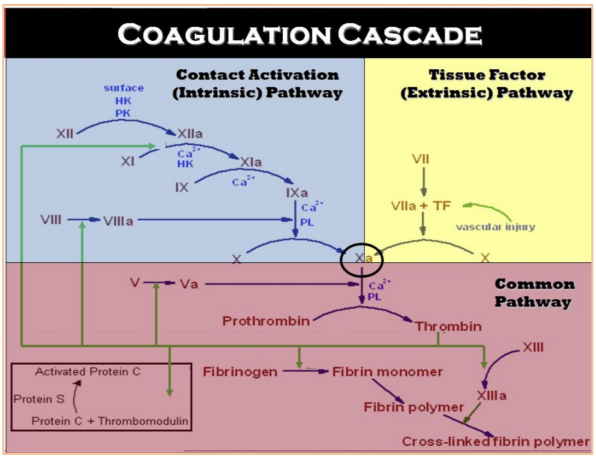
◀ Clotting factors: produced by the liver

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 Congenital deficiency → hemophilia A	Antihemophilic factor (AHF); antihemophilic globulin (AHG); antihemophilic factor A
Factor IX Congenital deficiency → hemophilia B	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	

for easy memorization

01.Freshers- **Fibrinogen**
02.Party- **Prothrombin**
03.Today- **Thromboplastin**
04.Come on- **Calcium**
05.Let's- **Labile factor**
07.Sing- **Stable factor**
08.And- **Anti Haemophilic factor**
09.Call the- **Christmas factor**
10.Seniors- **Stuart prower factor**
11.Please- **PTA**
12.Have- **Hageman factor**
13.Fun- **Fibrin stabilizing factor**

◀ Coagulation cascade:

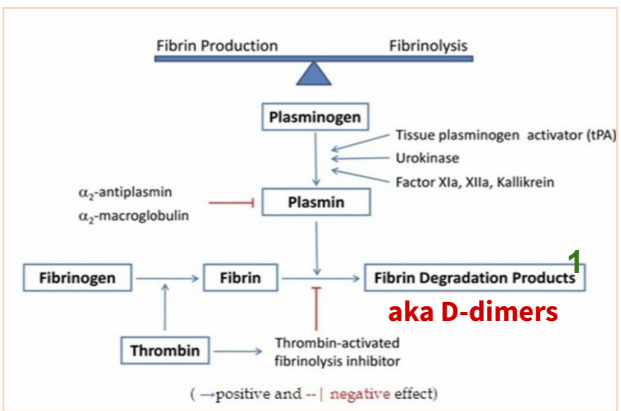


- The intrinsic pathway gets activated when the blood vessel gets injured. It starts by the activation of factor 12 when it comes in contact with the Subendothelial collagen of the injured vessel.
- To prevent further coagulation: 1) platelet inhibitors 2) protein C & S: they deactivate factor 5 & 8

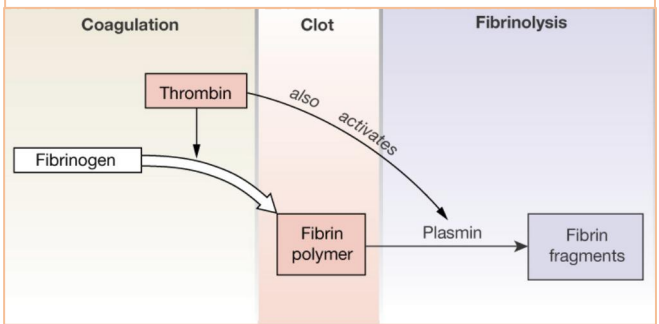
What are the VitK dependent factors? II, VII, IX, X, proteins C & S

Activation of factor 10 is the goal of initiation of extrinsic and intrinsic pathways

◀ Fibrinolysis :



Overall process:



1-Fibrin degradation products can sometimes increase as a result: of severe infections, leukemia (M3) and will ultimately lead to consumption of coagulation factors and disseminated intravascular coagulation (DIC)

Lab tests

LABORATORY EVALUATION
(to know the source of bleeding)

- PLATELET COUNT
- PROTHROMBIN TIME (PT)
- THROMBIN TIME (TT)
- BLEEDING TIME (BT)
- PARTIAL THROMBOPLASTIN TIME (PTT)

Platelet count:

- 100,000 - 400,000 CELLS/MM3 (NORMAL)
- < 100,000 (Thrombocytopenia " low platelet count ")
  - 50,000 - 100,000 (Mild Thrombocytopenia)
  - < 50,000 (Severe Thrombocytopenia)

Prothrombin time (PT):

- Measures the effectiveness of the **extrinsic** pathway.
- NORMAL VALUE **(10-15 SECS)**
- Prothrombin time tests the extrinsic and final common pathways

Prolongation in: (MCQ)

- Liver disease.
- vitamin K antagonism (i.e. **warfarin**) and deficiency
- Disseminated intravascular coagulation
- **Factor VII, X, V, II and fibrinogen defect.**

Bleeding time :

PROVIDES ASSESSMENT OF PLATELET COUNT AND FUNCTION NORMAL VALUE **(2-8 MINUTES.)**

Partial Thromboplastin time(PTT) :

- Measures Effectiveness of the **Intrinsic** Pathway.
- NORMAL VALUE **(25-40 SECS)**
- Activated partial thromboplastin time Tests the intrinsic and common pathways

Prolongation in:

- Liver disease.
- Disseminated intravascular coagulation.
- **Heparin therapy.**
- Vitamin K antagonism or deficiency.
- **Factor XII, XI, IX, VIII, X, V, II, and fibrinogen defect.**

Thrombin time(TT) :

- Time needed for thrombin to convert fibrinogen (soluble) to stable fibrin.
- A Measure of **Fibrinolytic Pathway**.
- NORMAL VALUE 9-13 SECS.
- Evaluate fibrinogen and for inhibition of thrombin action.

Prolongation in:

- Hypofibrinogenaemia.
- Dysfibrinogenaemia
- **Heparin therapy**.
- Disseminated intravascular coagulation.

Hypofibrinogenaemia :
Congenital deficiency which has problems with stabilizing clot, hence once they start to form the clot, bleeding happens again.
Dysfibrinogenaemia:
is a coagulation (clotting) disorder characterized by having an abnormal form of fibrinogen. Having abnormal fibrinogen results in defective clot formation and can cause an increased or decreased ability to clot.

CONGENITAL BLEEDING DISORDERS

◀ Hemophilia :

- An inherited bleeding disorder caused by deficiency of coagulation. **(The most common inherited disorder)**
  - It's 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. (Important)

Hemophilia	
Congenital :	**Acquired :**
• genetic mutation in F8 & F9 located on the long arm of X chromosome. • Observed commonly in **males** due to their hemizygous state . • Rarely in females due to (Heterozygous females as result from nonrandom X chromosome inactivation, **skewed Lyonization**[1], or the presence of other genetic abnormalities (**Turner Syndrome or X** autosomal translocations).	• Development of **autoantibodies** most commonly directed against **FVIII** – associated with pregnancy, malignancy, advanced age. • (anything that triggers the immune system to produce autoantibodies) such as lead poisoning and viral infections.

Types

- **Hemophilia A:** Inherited deficiency of **factor VIII** (8); an **X-linked recessive disorder** (male diseased and female carrier). It is protected from proteolysis in the circulation by binding to vWF.
- **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; 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).

Clinically	hematomas, hemarthrosis, bruising, bleeding **(mucosal, GI, GU, joint) deep bleeding. (traumatic bleeding)**
Diagnosis (IMP)	Increased aPTT, Factor level will be low, Mixing study (corrected in case of congenital only, not corrected in acquired), Normal VWF & PT.
Treatment	**Replacement of the deficient coagulation Factor** (recombinant or plasma derived) + Adjunctive therapy (Desmopressin (DDAVP levels of vwf will increase with this drug), Antifibrinolytic agents (Tranexamic Acid, Aminocaproic Acid), rFVIIa (with inhibitors).

1-It means the female has only one X and the other one is inactive .

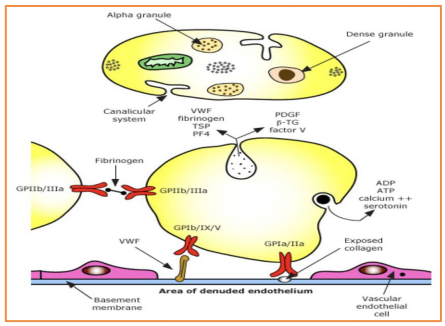
CONGENITAL BLEEDING DISORDERS

Baseline factor activity level[2] (MCQ) ★

- ★ **Severe Hemophilia** : defined as <1 % factor activity (<0.01 IU/mL). [3]
- ★ **Moderate Hemophilia** : defined as a factor activity level ≥1 % of normal and <5 % of normal (≥0.01 - <0.05 IU/mL).[4]
- ★ **Mild Hemophilia :** defined as a factor activity level ≥5 % of normal and <40 % of normal (≥0.05 - <0.40 IU/mL).[5]

◀ Von Willebrand Disease :

- ★ **The most common bleeding disorder.**
- ★ Inherited VWD is classified into Three types.
- ★ Defect of Von Willebrand Factor:
  - Quantitative (type 1 & 3)
  - Qualitative (type 2)
- ★ **Autosomal dominant**. (MCQ)
- ★ **The Normal function of VWF:**
  - **Mediate platelet adhesion.**
  - **Stabilize factor VIII** in circulation.[1]
  - Localize factor VIII to site of vessel injury.
- **Congenital :** autosomal dominant (most types), recessive (rarely).
- **Acquired :**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)



Classification of von Willebrand disease ★

Ristocetin-Induced platelet aggregation; a way to test PLT function

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

★ VWF func :
1- form an adhesive bridge between platelets and injured vascular epithelium.
2- carrier for factor VIII.
3- form a bridge between adjacent platelets allowing them to bind together and effectively form a platelet plug at sites of endothelial injury .

group F dr focused on the highlighted while males dr said you don't need to know the details

★ Diagnosis

- Normal aPTT in (Type 1 & 2).
- prolonged aPTT in (Type 2N, 2B, & 3)
- vWF:Ag.
- vWF:RCo.
- vWF multimers (to differentiate subtypes)
- FVIII assay (low in 2N & 3).
- Plt count (low in 2M).

&

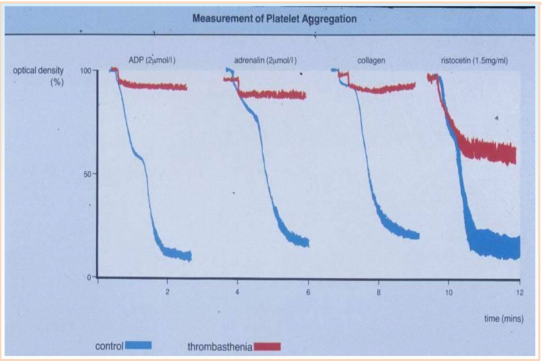
Treatment

- Replacement of exogenous vWF concentrate.
- Desmopressin (DDAVP intranasal)
  Antifibrinolytic agents (Tranexamic Acid Aminocaproic Acid).
- Conjugated Estrogens & oral contraceptive Agents (for menorrhagia) .

1- factor VIII it is imp for the intrinsic pathway + adhesion to vascular injury to allow the PLT to underline the clotting factor .
2- By knowing the Baseline factor activity level we can manage the haemophilic patient according to these definitions .
3- They need **regular transfusion** /replacement of the factor to prevent any serious bleeding .
4-they don't suffer from frequent bleeding so they can have factor **replacement at time of bleeding .**
5- **Minimal need** for factor replacement.

CONGENITAL BLEEDING DISORDERS

◀ Platelet aggregometry:



- Function of PLT depend on the secretion of certain substrates from the granules . Abnormality in the granules → "platelet function difficulty" or what is called "thrombasthenia" in which they will be unable to aggregate normally and give very weak wave (Red) while the blue waves are normal.
- To confirm, test for platelet ristocetin activity. In case of VWF disease all will be normal except ristocetin.

◀ Comparison between haemophilia and VWD :

	Hemophilia A	Factor IX deficiency	Von Willebrand
inheritance	Sex linked	Sex linked	Dominant (incomplete)
Main sites of hemorrhage	Muscle,joints,post-trauma or postoperative	Muscle,joints,post-trauma or postoperative	**Mucous membranes,** skin cuts, post-trauma or postoperative
Platelet count	Normal	Normal	Normal
Bleeding time	Normal	Normal	Prolonged
Prothrombin time	Normal	Normal	Normal
Partial thromboplastin time	**Prolonged**	**Prolonged**	**Prolonged or Normal**
Factor VIII	Low	Normal	May be moderately reduced
Factor IX	Normal	Low	Normal
vWF	Normal	Normal	**Low**
Ristocetin-induced platelet aggregation	Normal	Normal	**Impaired**

1- It stimulates endogenous production of VWF .

Platelets Disorders

◀ Plt Disorders (Quantitative) : Just know the name

Causes of Thrombocytopenia:

Falsely low platelet counts (ie, pseudothrombocytopenia)
In vitro platelet clumping caused by EDTA-dependent agglutinins
In vitro platelet clumping caused by an insufficiently anticoagulated specimen
In vitro platelet clumptin caused by glycoprotein IIb/IIIa inhbitors (eg, abciximab) (NOTE: these can also cause true thrombocytopenia)
Giant platelets counted by automated counter as white blood cells rather than platelets
Common causes of thrombocytopenia
Drug-induced thrombocytopenia
Heparin (NOTE: special case, also can cause thrombosis)
Quinine (as in over-the-counter preparations for leg cramps; also in beverages)
Sulfonamides (eg, trimethoprim-sulfamethoxazole [Bactrim; Septra])
Acetaminophen (Tylenol, Panadol)
Cimetidine (Tagamet)
Ibuprofen (Advil, Motrin)
Naproxen (Aleve, Midol)
Ampicillin (Omnipen, Apo-Ampi)
Piperacillin (Pipracil, Zosyn)
Vancomycin (Vancocin)
Glycoprotein IIb/IIIa inhibitors (abciximab [ReoPro], tirofiban [Aggrastat], eptifibatide [Integrilin])
Food and beverages
Quinine-containing beverages (tonic water, Schweppes bitter lemon)
Infections
HIV

Pseudothrombocytopenia or spurious thrombocytopenia is an in-vitro sampling problem which may mislead the diagnosis towards the more critical condition of thrombocytopenia. The phenomenon occurs when the anticoagulant used while testing the blood sample causes clumping of platelets which mimics a low platelet count.

Other causes of thrombocytopenia
Myelodysplasia
Suspected in older patients, in whom a bone marrow biopsy may be appropriate
Cancer with disseminated intravascular coagulation
Cancer with bone marrow infiltration or suppression (eg, lymphoma, leukemia, some solid tumors)
Paroxysmal nocturnal hemoglobinuria (PNH)
Thrombotic thrombocytopenic purpura (TTP) or hemolytic uremic syndrome (HUS)
TTP is a syndrome that can include thrombocytopenia, microangiopathic hemolytic anemia, fever, renal failure, and neurologic symptoms. However, patients with TTP commonly present with thrombocytopenia and anemia alone.
HUS is typically a disorder of young children following infection with a Shiga-toxin producing E. coli.
Antiphospholipid syndrome (APS)
Aplastic anemia
Congenital thrombocytopenias
An important consideration, especially in young patients who do not respond to treatment. Some specific syndromes are listed. However, many patients appear to have autosomal dominant thrombocytopenia with no other clinical features.
Von Willebrand disease type 2B
Wiskott-Aldrich syndrome
Alport syndrome
May-Hegglin anomaly
Fanconi syndrome
Bernard-Soulier syndrome
Thrombocytopenia absent radius syndrome

Infections
HIV
Hepatitis C
Epstein-Barr virus (EBV; can be associated with infectious mononucleosis)
H. pylori (suspected in patients with symptoms of dyspepsia or peptic ulcer disease)
Sepsis with disseminated intravascular coagulation (DIC)
Intracellular parasites (eg, malaria, babesia)
Hypersplenism due to chronic liver disease
Alcohol
Nutrient deficiencies (eg, vitamin B12, folate, copper) Dr : MCQ
Rheumatologic/autoimmune disorders (eg, systemic lupus erythematosis, rheumatoid arthritis)
Pregnancy
Gestational thrombocytopenia
Preeclampsia
HELLP syndrome (hemolysis, elevated liver function tests, low platelets)

Infection + DIC or febrile neutropenia → don't give vancomycin

When the spleen is active it eats megakaryocytes.

Gestational thrombocytopenia happens because the body considers the baby a foreign body and develops autoantibodies that affect the platelets. Usually resolves after delivery.

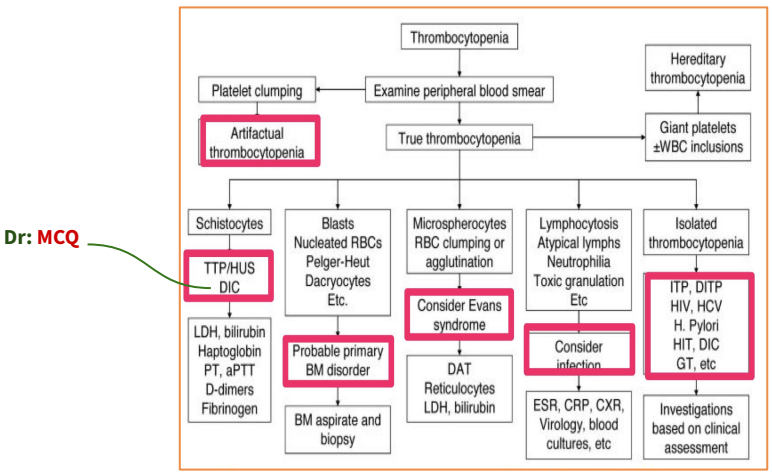
- Platelet count < 100 is thrombocytopenia : between 50-100 is **mild**, less than 50 is **severe**, less than 30 → **no surgical procedures.**

Platelets Disorders

◀ Approach to Thrombocytopenia

I have a patient's CBC that shows thrombocytopenia.
-First ask to examine the peripheral blood smear under the microscope, if there's platelet plugging, then there's pseudothrombocytopenia, & ask for the CBC to be repeated on citrate.
-If it is true thrombocytopenia:

- Look in the peripheral blood morphology, if there is:
  - Fragmented RBCs, then this is consumption coagulopathy, which means there is a problem in the blood leading to more coagulation and platelet consumption. This is present in TTP, HUS, & DIC. It is diagnosed by elevated LDH & bilirubin, low haptoglobin, prolonged PT & aPTT.
  - If you take a BM biopsy and find blast cells, then it means that there is a problem in the factory (bone marrow; possibly leukemia) **Refer to Hematologist.**
  - Clumped or agglutinated RBCs → consider Evans syndrome (autoimmune hemolytic anemia with autoimmune thrombocytopenia; characterized by reticulocytosis & +ve Coomb's test, increased LDH & bilirubin)
  - Elevated levels of lymphocytes/neutrophils → consider an infection
  - Isolated thrombocytopenia → consider ITP (idiopathic thrombocytopenia) or viral infection



◀ Immune Thrombocytopenic Purpura (ITP):

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

2 **Secondary :** Associated with(disease/drug exposure) so look for any **Viral** (HIV, HCV, HBV, EBV, CMV, Parvovirus), SLE,APLS, H. Pylori Infection, If you didn't find any of the previous causes look for: Chronic Lymphocytic Leukemia (CLL), Hodgkin Lymphoma, AIHA .

Clinically

- insidious onset of mucocutaneous bleed (Ecchymosis , purpura)
- M:F (3:1).

Diagnosis

- **Dx of exclusion**
- no robust clinical or Lab parameters.
- **Typically CBC (Isolated low PLT <100.000)** with normal PT/PTT.
- 10% have ITP + AIHA (Evans Syndrome).
- PBS (Large Plts).
- Anti-Plt AB (not useful).

RX

- Rarely indicated if PLT **> 50.000** unless bleeding, trauma/surgery, anticoag, comorbidities .
- Treatment options:
  - Steroids.
  - IVIG.
  - Splenectomy.
  - TPO agonists (Romiplostim, Eltrombopag).

Platelets Disorders

◀ Immune Thrombocytopenic Purpura (ITP) Treatment :

- **First line treatment:**
  - **Steroids**
  - **IVIG**

It serves as a confirmatory step as well, if the pt doesn't respond to the steroids, you have to revise your dx.

- **Second line treatment:**
  - Splenectomy it predisposes the patient to opportunistic infections.
  - Rituximab
- **Refractory cases :**
  - Romiplostim or eltrombopag.

IF FAILED ALL THE ABOVE GO FOR STEM CELL TRANSPLANT .

Approach	Treatment	Notes
First-line	**Steroids:** prednisone 0.5–2 mg/kg/d PO tapered ~4 wk vs. dexamethasone 40 mg PO × 4 d	↓ Mϕ FcR & ↓ anti-plt Ab 70–90% initial response ~20% sustained remission
	Anti-Rh(D) Ig 75 μg/kg/d IV	For Rh(D) ⊕ Pts w/ spleen Ab-coated RBCs overwhelm Mϕ FcR
	IVIg (1 g/kg/d IV × 2–3 d) *consider if need rapid ↑ in plt*	Blocks Mϕ FcR, ↓ anti-plt Ab Up to 80% initial response
	Splenectomy *? for ITP >6 mo)*	~65% long-term remission
Second-line	Rituximab (anti-CD20) ± dex	anti–B-cell Ab
	Romiplostim or **eltrombopag**	TPO-R agonists → ↑ plt prod
	Azathioprine, cyclophosphamide	Immunosuppressants
	Danazol, vincristine	↓ plt clearance
Bleeding	Aminocaproic acid	Inhibits plasmin activation
	Methylprednisolone 1g/d IV × 3 d	See above
	IVIg	See above
	Platelet transfusion	Given w/ IVIg or anti-Rh(D)
Refractory	Romiplostim or eltrombopag	See above
	Autologous HSCT	Limited data, investigational

◀ Disseminated Intravascular Coagulation (DIC) :

Etiology :

- Trauma
- Infection
- Shock
- Obstetric Complications
- Malignancy (esp APML) (**M3**)

Pathogenesis :

Massive activation of coagulation **cascade** that overwhelms control mechanisms → **Excess thrombosis**

→ Acute consumption of coagulation factors & plt [1] → **Bleeding**

Diagnosis & Treatment

Diagnosis

- Prolonged PT and aPTT.
- decreased fibrinogen(may be N b/c acute phase)[2]
- low plt.
- high LDH.
- +ve Schistocytes
- low haptoglobin
- +ve D- Dimer/FDP
- Patient comes with fever & bleeding everywhere

Treatment

- Treat underlying process .
- fresh frozen plasma (FFP)
- Cryoprecipitate (Goal Fibrinogen > 100 mg/dL)
- PLT Tx .

◀ Plt Disorders (Qualitative) :

❑ **ACQUIRED PLT FUNCTIONAL (normal numbers) DISORDERS:**

1. Congenital Liver Disease
2. Cardiopulmonary Bypass (cause plugging in the metallic valve used)
3. Uremia (by the toxins in renal failure)
4. Dysproteinemia (Multiple Myeloma or Waldenstrom Macroglobulinemia)
5. Myeloproliferative Disorders (MPDs)
6. Diabetes Mellitus .
7. Acquired **Glanzmann** thrombasthenia.(imp)

1-Consumption coagulopathy means more coagulation more consumption of PLT so more thrombosis , at the same time they will have bleeding because they consume all the PLT .

2-Fibrinogen is an acute phase reactant (which is high in acute inflammation) so if a DIC patient has high fibrinogen this indicate he has severe infection. so we can see it as high or low in DIC.

Platelets Disorders

◀ Plt Disorders (Qualitative) :

Bernard-Soulier Syndrome → Genetic GPIb deficiency
Glanzmann thrombasthenia → Genetic GPIIb/IIIa deficiency

❑ **INHERITED DISORDERS OF PLT FUNCTION:** Know only the names (not imp)

1. **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 Plt Syndrome).
2. **Storage Pool Disorders** such as Hermansky Pudlak Syndrome (HPS)
3. Wiskott-Aldrich syndrome .
4. **Glanzmann thrombasthenia** (aggregate in response to ristocetin) .
5. Platelet release disorders.
6. Glycoprotein VI defects
7. Sticky platelet syndrome .
8. Congenital Deficiency of the ADP receptor P2Y 12.
9. Scott syndrome.

◀ Approach to Pt with Potential Bleeding :

Two important points:

1. Detailed Pt & Family Medical History (Crucial & Vital regardless of the prior Lab testing)
2. Laboratory Testing.

1. Detailed Pt & Family Medical History

- Establish likelihood of a bleeding disorder , guide laboratory testing
- Early in the newborn period (problem during circumcision, or bleeding in females)
- After hemostatic Challenges (Delivery, injury, trauma, surgery, invasive dental procedure, menstruation).
- Frequency & pattern .
- Duration :
  - Symptoms onset (congenital vs. acquired) .
  - Time required for cessation.
- **Sites of bleeding (specific or multiple) :** (Very important)

Primary Hemostasis Defects (PLT or vW Factor) →
Mucocutaneous Bleeding :
- Easy bruising
- Epistaxis
- Menorrhagia

Secondary Hemostasis Defects (Clotting Factors deficiency) →
Deep Tissue Bleeding :
- Joint (Hemarthrosis)
- Muscles
- CNS (intracerebral hemorrhage)

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

Drugs Used for Clotting Disorders

you should know them to rule them out from the history .

Anticoagulants

- Direct Thrombin Inhibitors
- Indirect Thrombin Inhibitors
- Vitamin K epoxide reductase Inhibitor.
- Direct Xa Inhibitors

Generic Name	Trade Name	Half Life
Dabigatran	Pradaxa	12 – 28 hr
Argatroban	Acova	39 – 51 min
Lepirudin	Refludan	1.3 hr
Bivalirudin	Angiomax	25 – 57 min
Unfractionated Heparin (UFH)	.....	
LMWH - Enoxaparin	Clexan	4.5 – 7 hr
LMWH - Tinzaparin	Innohep	3 – 4 hr
LMWH - Deltaparin		
Fondaparinux	Arixtra	17 – 21 hr
Warfarin	Coumadin	7 – 11 hr
Rivaroxaban	Xarelto	5 – 13 hr
Apixaban	Eliquis	5 – 13 hr
Endoxaban	Savaysa	10 – 14 hr

Antiplatelet

- Prostaglandin/COX Inhibitors
- Glycoprotein IIb/IIIa Inhibitors
- $P2Y_{12}$ ADP Inhibitors

Generic Name	Trade Name	Half Life
Aspirin	.....	24 – 72 hr
Abciximab	Reopro	72 hr
Eptifibatide	Integrilin	4 hr
Tirofiban	Aggrastat	4 hr
Clopidogrel	Plavix	6 hr
Cangrelor	Kengreal	3 – 6 min
Prasugrel	Effient	7 – 15 hr
Ticlopidine	Ticlid	13 hr
Ticagrelor	Brilinta	7- 9 hr

Thrombolytics

- Plasminogen Activators

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

Plasminogen → Plasminogen activator → Plasmin → Fibrin clot → Fibrin degradation products

-Heparin is monitored by PTT whereas clexan (enoxaparin) is monitored by factor Xa.
-one of the rare side effects of heparin is HIT, it can be caused by enoxaparin but it's less severe.
-if a patient gets HIT, stop heparin or enoxaparin and start them on dabigatran or argatroban as they don't cause HIT
-Renal adjustment is important when administering clexan (enoxaparin) in renal impairment.

Approach to Pt with Potential Bleeding

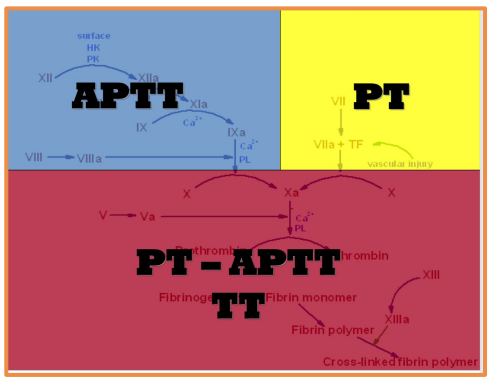
2. Laboratory Testing

◄ Screening Tests :

1) **CBC (Platelet count) .**
2) **Prothrombin Time (PT) :** measures F VII, X, V, II, I - (N Time 10-14 secs) .
3) **International Normalized Ratio (INR) :** the ratio of a pt's PT to a normal (control) sample, raised to the power of the ISI value for the control sample used.
4) **Activated Partial Thromboplastin Time (aPTT or PTT) :** measures F XII, XI, IX, VIII, X, V, II, I - (N Time 30 – 40 secs) .
5) **Thrombin (Clotting) Time (TT) :** sensitive to deficiency of Fibrinogen or inhibition of thrombin - (N 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.

◄ Causes of prolonged coagulation profile : ★ SUM



Test result		Causes of test result pattern
PT	aPTT	
Prolonged	Normal	**Inherited**
		Factor VII deficiency ←
		Acquired
		Mild vitamin K deficiency ←
		Liver disease
		Warfarin administration ←
		Acquired inhibitor of factor VII ←
		Lupus anticoagulant (more commonly causes isolated prolonged aPTT; may be associated with thrombosis rather than bleeding)

Test result		Causes of test result pattern
PT	aPTT	
Normal	Prolonged	**Inherited**
		Deficiency of factors VIII, IX, or XI ←
		Deficiency of factor XII, prekallikrein, or HMW kininogen (not associated with a bleeding diathesis)
		von Willebrand disease (variable)
		Acquired
		Heparin administration ←
		Direct thrombin inhibitor administration (eg, argatroban, dabigatran)
		Inhibitor of factors VIII, IX, XI, or XII
		Acquired von Willebrand disease
		Lupus anticoagulant (may be associated with thrombosis rather than bleeding) ←

Test result		Causes of test result pattern
PT	aPTT	
Prolonged	Prolonged	**Inherited**
		Deficiency of prothrombin, fibrinogen, or factors V or X ←
		Combined factor deficiencies
		Acquired
		Liver disease
		Disseminated intravascular coagulation ←
		Supratherapeutic doses of anticoagulants
		Severe vitamin K deficiency ←
		Combined heparin and warfarin administration
		Direct factor Xa inhibitor administration (eg, rivaroxaban, apixaban, edoxaban)
		Fondaparinux administration (slight prolongation)
		Inhibitor of prothrombin, fibrinogen, or factors V or X
		Primary amyloidosis-associated factor X deficiency
		Anticoagulant rodenticide poisoning

Approach to Pt with Potential Bleeding

◄ Specialized Tests :

Mixing Study (one to one mix of Pt's plasma & known normal standard plasma, only if PT of aPTT prolonged) used in case of antibody produced against the clotting factor (Acquired hemophilia) .

- Corrected → clotting factor deficiency (risk of bleed).
- Not corrected → inhibitors (directed against specific factor or global inhibitors " **Lupus Inhibitor**, risk of thrombosis ").

1. **PLT Function Assay (PFA - 100):** assess PLT function
   - ➢ Specificity > 90 % for severe PLT dysfunction of vWD (vWF plasma levels < 25%)
   - ➢ Sensitivity > 24 – 41 % (low) in mild PLT secretion defect or Storage Pool Disease > (not screening tool).
2. **PLT Aggregation Tests:** (5 external aggregating factors; ADP, Collagen, Ristocetin, Arachidonic Acid, Adrenaline).
3. **Von Willebrand Factor** (Antigen & Activity).
4. **Factor XIII assay (F XIII Deficiency >> normal PT & PTT).**
   a. Severe visceral bleeding (e.g. intracerebral hemorrhage) with normal labs? That's probably Factor 13 deficiency, it's an autosomal dominant inherited disorder.
   b. Tx: Every 3wks factor XIII concentrate or FFP.
5. **Human Plasminogen Activator Inhibitor (PAI-1) .**
6. **Alpha 2 AntiPlasmin Inhibitor (α2 AP).**

◄ Take home messages:

- 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

Extra info (from Doctor's slides)

◀ Management in the Perioperative Stage:

❖ **Management of Bleeding PT:**

- 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.

1. **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.

2. **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.

3. **Antifibrinolytic Agents (Tranexamic Acid, epsilon Aminocaproic Acid)** may be helpful in reducing bleeding in pts with disordered plt function following dental extraction.

4. **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.

5. **Erythropoietin** used successfully in uremic pts to both reduce and prevent bleeding.

6. **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.

Extra info (from Doctor's slides)

◀ Preoperative Management of Agents Affecting Hemostasis:

- **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 pts undergoing surgery with high bleeding risk (eg, intracranial, spinal, urologic) or if neuraxial anesthesia is to be used).
  - Heparin / LMWH Bridging considered >> Pts with very high or high thromboembolic risk.
- **Heparin:**
  - 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.

lass 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				

Extra info (from Doctor's slides)

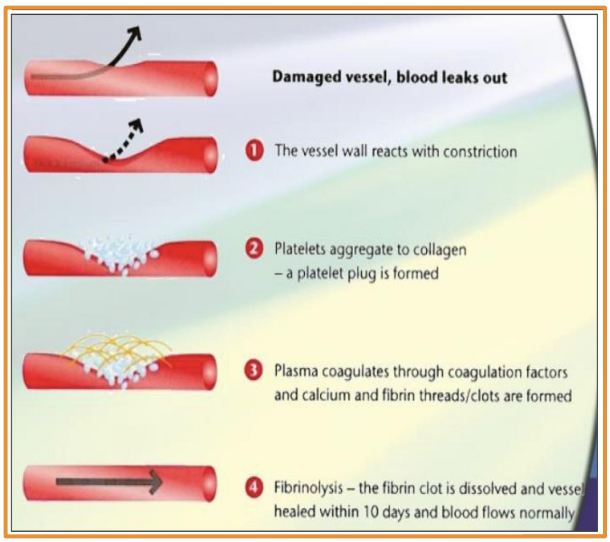
Coagulation Factor Levels Required For Hemostasis:

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

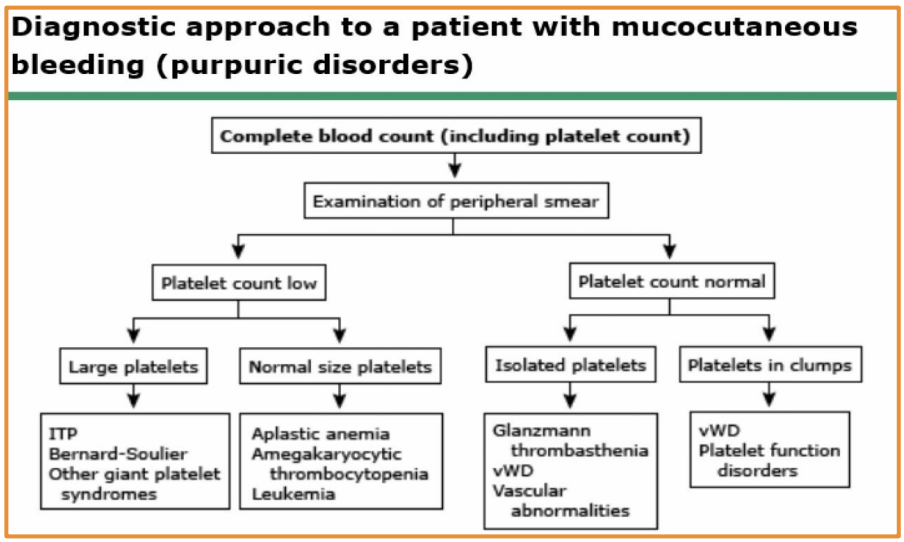
Inhibitors:

1. **Antithrombin III**
   - A serine 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.

Hemostatic Phases:



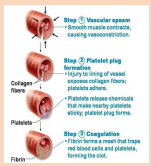
Diagnostic Approach to Platelet Disorders:



Summary

Overview of Hemostasis

Hemostasis



- The process through which bleeding is controlled.

Primary Hemostasis:
- Endothelium Injury
- Platelet plug
- Von Willebrand Factor

Secondary Hemostasis:
- Clotting Factors
- Soluble Protein Fibrinogen converted to insoluble Fibrin.

Lab tests

Platelet count (Normal: 150 – 400 x 10^9).
< 100,000 (Thrombocytopenia)
- 50,000 - 100,000 (Mild): Follow up
- < 50,000 (Severe): Needs intervention

- Platelets are produced in the Bone Marrow by fragmentation of the cytoplasm of megakaryocytes.
- **PLT Life Span (7 – 10 days).**

Prothrombin time (PT):
- Measures the effectiveness of the **extrinsic** pathway.
- NORMAL VALUE **(10-15 SECS)**

Partial Thromboplastin time :
- Measures Effectiveness of the **Intrinsic** Pathway.
- NORMAL VALUE **(25-40 SECS)**

Bleeding time :
- PROVIDES ASSESSMENT OF **PLATELET COUNT AND FUNCTION** NORMAL VALUE **(2-8 MINUTES)**

Thrombin time :
- A Measure of Fibrinolytic Pathway.
- NORMAL VALUE 9-13 SECS.

Bleeding disorders

Definition

- Bleeding disorders are a group of disorders that share the inability to form a proper blood clot. They are characterized by extended bleeding after injury, surgery, trauma or menstruation.

Primary hemostasis (only) disorders:
Characterized by Mucocutaneous bleeding - Petechial rash - Epistaxis - Menorrhagia.
Thrombocytopenia? First ask to examine the peripheral blood smear

Disease	Etiology	Diagnosis	Treatment
Quantitative			
Immune Thrombocytopenic Purpura (ITP)	- Primary: **Isolated thrombocytopenia** due to immune platelet destruction (auto AB to megakaryocytes) - Secondary.	**Diagnosis of exclusion.** • CBC (isolated thrombocytopenia) • PBS (large platelet) • Antiplatelet antibodies (Anti-GpIIb/IIIa)	**No bleeding**, count > 50,000: **NO treatment** **- 1st line:** • **Steroids & IVIG** **- 2nd line:** Splenectomy & Rituximab **- Refractory:** Romiplostim.
Qualitative			
Bernard soulier	Autosomal recessive Deficient platelet **GP**Ib-IX	Peripheral smear: Giant platelets • ↓ Platelets • Abnormal ristocetin cofactor assay	
Glanzmann thrombasthenia	Autosomal recessive Deficient platelet **GP**IIb-IIIa	Normal platelets Abnormal results on platelet aggregation testing confirm the diagnosis.	
Secondary or Drug induced	**Uremia (Renal disease)** drugs: e.g. aspirin or clopidogrel	•	Treat underlying cause Stop the drug.

Summary

Bleeding disorders *cont.*

Secondary hemostasis (only) disorders:
Characterized by hematomas, hemarthrosis, bruising, bleeding (mucosal, GI, GU, joint) deep bleeding.

Disease	Etiology	Diagnosis	Treatment
Hemophilia A	- Congenital: Inherited deficiency of **factor VIII** an **X-linked recessive disorder** - Secondary: Development of **autoantibodies** most commonly directed against **FVIII** (ass. with pregnancy, malignancy, advanced age).	• **Factor VIII Assay: low.** • Mixing study (corrected) • Normal VWF & PT.	• **Replacement of the deficient coagulation Factor** • **Desmopressin** • **Antifibrinolytic agents (Tranexamic Acid, Aminocaproic Acid**
Hemophilia B	Inherited deficiency of factor IX; also called Christmas Disease; an **X-linked recessive disorder.**	• **Factor IX Assay: low** • Mixing study (corrected) • Normal VWF & PT.	
Hemophilia C	Inherited deficiency of factor XI ; also called Rosenthal Syndrome; an **autosomal recessive** disorder (Ashkenazi Jews).	• **Factor XI Assay: Low** • Normal PT & PTT	
Factor XIII Deficiency		• **Factor XIII Assay: FXIII Deficiency** • Normal PT & PTT	

Baseline factor activity level

★ **Severe Hemophilia** : defined as <1 % factor activity (<0.01 IU/mL).
★ **Moderate Hemophilia** : defined as a factor activity level ≥1 % of normal and <5 % of normal (≥0.01 - <0.05 IU/mL).
★ **Mild Hemophilia :** defined as a factor activity level ≥5 % of normal and <40 % of normal (≥0.05 - <0.40 IU/mL).

Disorders not specific to one step of hemostasis.
Clinical features: Bleeding of Mucous membranes, skin cuts, post-trauma or postoperative

Disease	Etiology	Diagnosis	Treatment
Von Willebrand Disease	**(most common bleeding disorder)** Defect of Von Willebrand Factor: Quantitative (type 1 & 3) | Qualitative (type 2) **Clinical features: Bleeding of Mucous membranes,** skin cuts, post-trauma or postoperative		
	Congenital: Autosomal dominant. **Normal function of VWF:** **- Mediate platelet adhesion.** **Acquired :**rare, caused by autoantibodies	Normal aPTT in (Type 1 & 2). Prolonged aPTT in (Type 2N, 2B, & 3) vWF: Ag. FVIII assay (low in 2N & 3). Plt count (low in 2M).	**- Replacement of exogenous vWF concentrate.** **- Desmopressin** **- Antifibrinolytic agents (Tranexamic Acid, Aminocaproic Acid**
Disseminated Intravascular Coagulation	Trauma Septic shock Malignancy (esp APML) Major trauma	Prolonged PT and aPTT. decreased fibrinogen. Low plt. High LDH. Low haptoglobin.	- Treat underlying process . - fresh frozen plasma (FFP) - Cryoprecipitate

Summary

How to differentiate between bleeding disorders?						
Disorder	**Platelets**	**Bleeding time**	**INR**	**PT**	**aPTT**	**Other:**
Thrombocytopenia	↓	↑	**Normal**	**Normal**	**Normal**	-
Platelet dysfunction (e.g. aspirin therapy or uremia)	**Normal**	↑	**Normal**	**Normal**	**Normal**	-
Extrinsic pathway (e.g. Factor VII def.)	**Normal**	**Normal**	↑	↑	**Normal**	**Specific factor assay: Low** **Mixing study: correctable**
Intrinsic pathway (e.g. Hemophilia A, B & heparin therapy).	**Normal**	**Normal**	**Normal**	**Normal**	↑	-
Von Willebrand disease (vWD)	**Normal**	↑	**Normal**	**Normal**	**Normal/** ↑	**vWF assay: low (dominant)** **FVIII assay (low)**
Disseminated intravascular coagulation (DIC)	↓	↑	↑	↑	↑	-

Lecture Quiz

Q1:A 38-year-old woman presents with a 3-day history of fever and confusion. She was previously healthy and is taking no medications. She has not had diarrhea or rectal bleeding. She has a temperature of 38°C (100.4°F) and a blood pressure of 145/85. Splenomegaly is absent. She has no petechiae but does have evidence of early digital gangrene of the right second finger. Except for confusion the neurological examination is normal. Her laboratory studies reveal the following: Hemoglobin: 8.7 g/dL, Platelet count: 25,000/μL ,Peripheral smear: numerous fragmented RBCs, few platelets, LDH 562 IU/L(normal < 180), Creatinine: 2.7 mg/dL, Liver enzymes: normal, Prothrombin time/PTT/fibrinogen levels: normal. What is the most likely pathogenesis of her condition?

A- Disseminated intravascular coagulation
B- Antiplatelet antibodies
C- Failure to cleave von Willebrand factor multimers
D- Verotoxin-induced endothelial damage

Q2:A 25-year-old woman complains of persistent bleeding for 5 days after a dental extraction. She has noticed easy bruisability since childhood, and was given a blood transfusion at age 17 because of prolonged bleeding after an apparently minor cut. She denies ecchymoses or bleeding into joints. Her father has noticed similar symptoms but has not sought medical care. Physical examination is normal except for mild oozing from the dental site. She does not have splenomegaly or enlarged lymph nodes. Her CBC is normal, with a platelet count of 230,000. Her prothrombin time is normal, but the partial thromboplastin time is mildly prolonged. The bleeding time is 12 minutes (normal 3-9 minutes).
What is most appropriate way to control her bleeding?

A- Factor VIII concentrate
B- Fresh frozen plasma
C- Desmopressin (DDAVP)
D- Whole blood transfusion e. Single donor platelets

Q3: A patient with bacterial endocarditis develops thrombophlebitis while hospitalized. His course in the hospital is uncomplicated. On discharge he is treated with penicillin, rifampin, and warfarin. Therapeutic prothrombin levels are obtained on 15 mg/d of warfarin. After 2 weeks, the penicillin and rifampin are discontinued. Which of the following is the best next step in management of this patient?

A- Cautiously increase warfarin dosage.
B- Continue warfarin at 15 mg/d for about 6 months.
C- Reduce warfarin dosage.
D- Stop warfarin therapy.

Q4:A 70-year-old intensive care unit patient complains of fever and shaking chills. The patient develops hypotension, and blood cultures are positive for gram-negative bacilli. The patient begins bleeding from venipuncture sites and around his Foley catheter. Laboratory studies are as follows: Hct: 38% WBC: 15,000/μL Platelet count: 40,000/μL (normal 150,000-400,000) Peripheral blood smear: fragmented RBCs PT: elevated PTT: elevated Plasma fibrinogen: 70 mg/dL (normal 200-400). Which of the following is the best course of therapy in this patient?

A- Begin heparin.
B- Treat underlying disease.
C- Begin plasmapheresis.
D-Begin red blood cell transfusion

Answers: Q1:C | Q2:C | Q3:C | Q4:B

Answers Explanation File!

GOOD LUCK !

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