Medicine
TEAM 437

MED437
KING SAUD UNIVERSITY

Bleeding disorders

Outlines:

- 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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Resources :

- 437 slides | Not Same 436's slides
- Teamwork 436
- Doctor notes | Prof.Ghada ElGohary
- QWord bank
- Amboss

What is a 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.

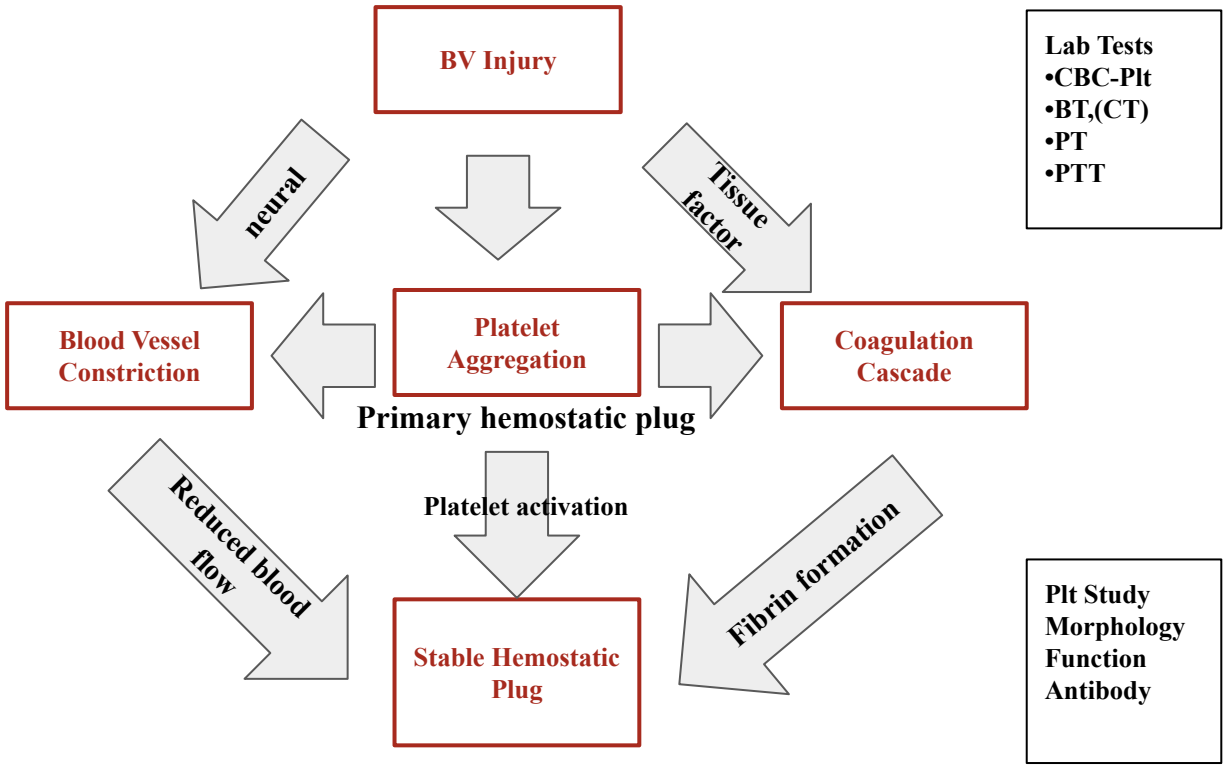
This video would be helpful:
https://youtu.be/GAcAPDVD3C0

Hemostasis

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

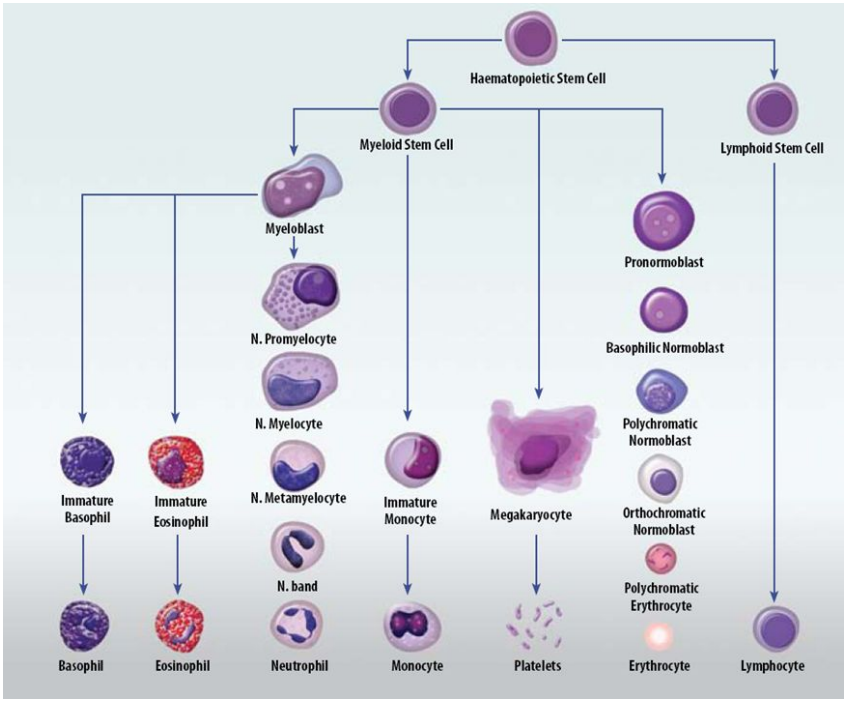
A dynamic interplay between

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



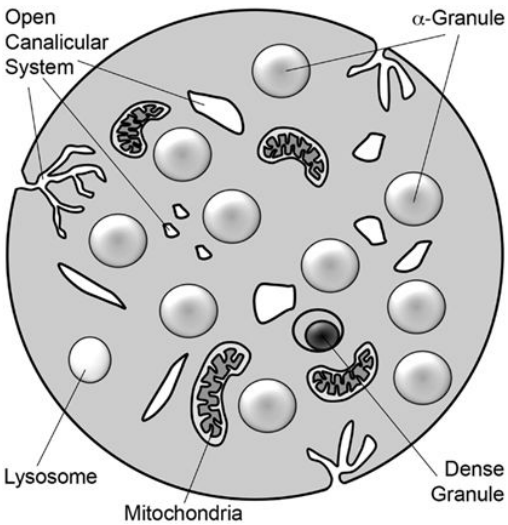
PLATELETS

- 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)
- Thrombopoietin is the major regulator of Plt production via c-MPL receptor (produced by Liver & Kidney)
- Normal PLT counts (150 – 400 x 10^9) (Important)
- PLT Life Span (7 – 10 days)



PLTs Ultrastructure

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



3 types of storage granules

α Granules

- Clotting Factors
- VWF
- PDGF
- ILGF1

Dense Granules (δ Granules)

- ADP & ATP
- Serotonin
- Histamine
- Ionized Ca

Lysosomes

- Hydrolytic enzymes

PLTs Functions

I.**Adhesion (PLT – Vessel Wall)** <- 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**)**

II.**Aggregation (cross linking of PLT – PLT)** <- VWF & Fibrinogen through GP IIb/IIIa receptors

III.**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.

PLTs Inhibitors

PLT Function Inhibitors

Prostacyclin (PGI_2);

- synthesized by vascular endothelial cells
- potent inhibitor of PLT aggregation & causes vasodilation by rising cAMP
- prevents Plt deposition on normal vascular endothelium

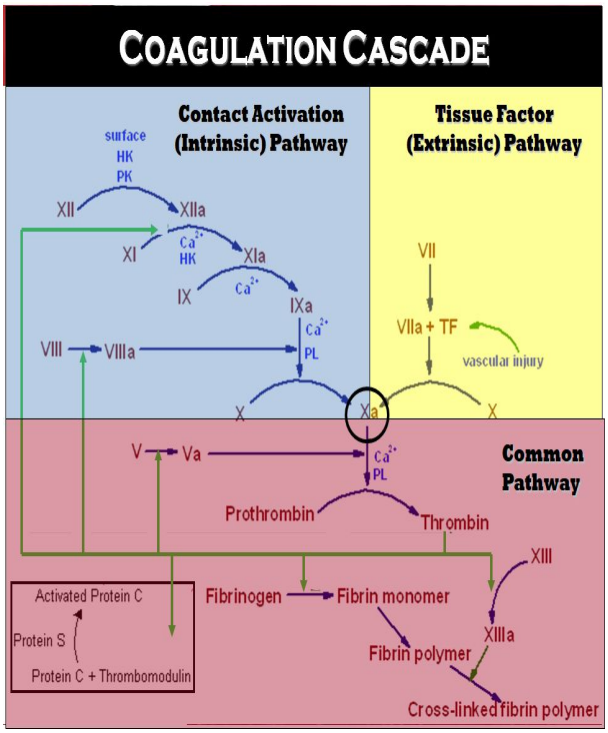
Nitric Oxide (NO);

- released from endothelial cells, macrophages, & Plt
- inhibit Plt activation & promotes vasodilation

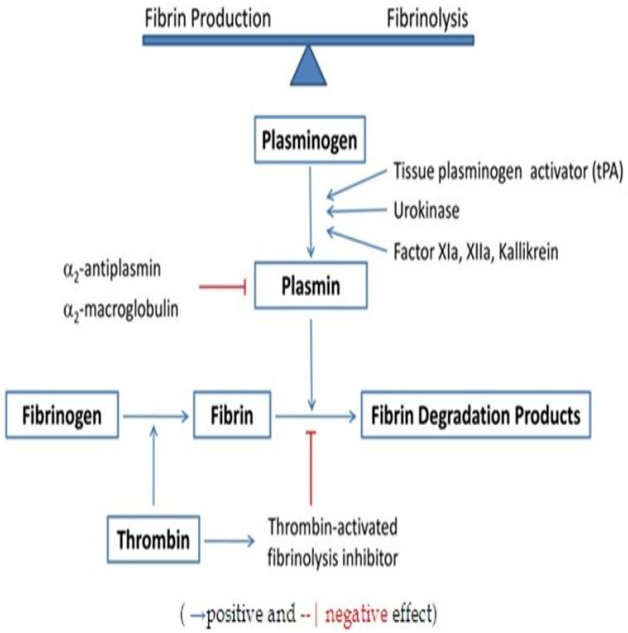
Clotting Factors

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	



Fibrinolysis



Great video explaining coagulation cascade: https://youtu.be/JoPQEDt1b0w

HEMOSTASIS

DEPENDENT UPON:

- Vessel Wall Integrity (because we need vascularity. Vasculitis and CT disorders will affect that causing bleeding tendency)
- Adequate Numbers of Platelets
- Proper Functioning Platelets
- Adequate Levels of Clotting Factors (Any defect of any of the factors will cause massive bleeding)
- Proper Function of Fibrinolytic Pathway

Hemostatic Phases

I. Vascular Phase:
release of locally active vasoactive agents (Endothelin, Thromboxane A2, Fibrinopeptides) □ *Vasoconstriction* at the site of injury □ reduced blood flow

II. Platelet Phase: Plt Adhesion & Aggregation (via VWF, ADP, TXA2) □ formation of *PLT Plug*

III. Plasma Coagulation Phase: Propagation of the clotting process by the coagulation cascade □ formation of *Fibrin Clot*

IV. Fibrinolysis Phase: Termination of clotting by antithrombotic control mechanisms & removal of the clot

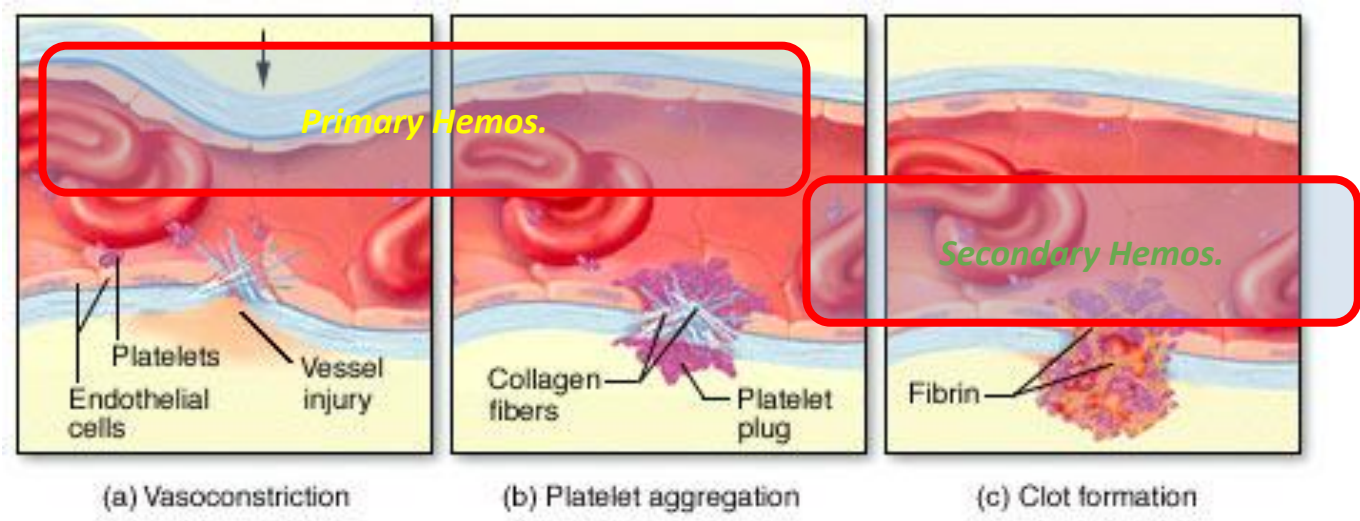
Primary Hemostasis:

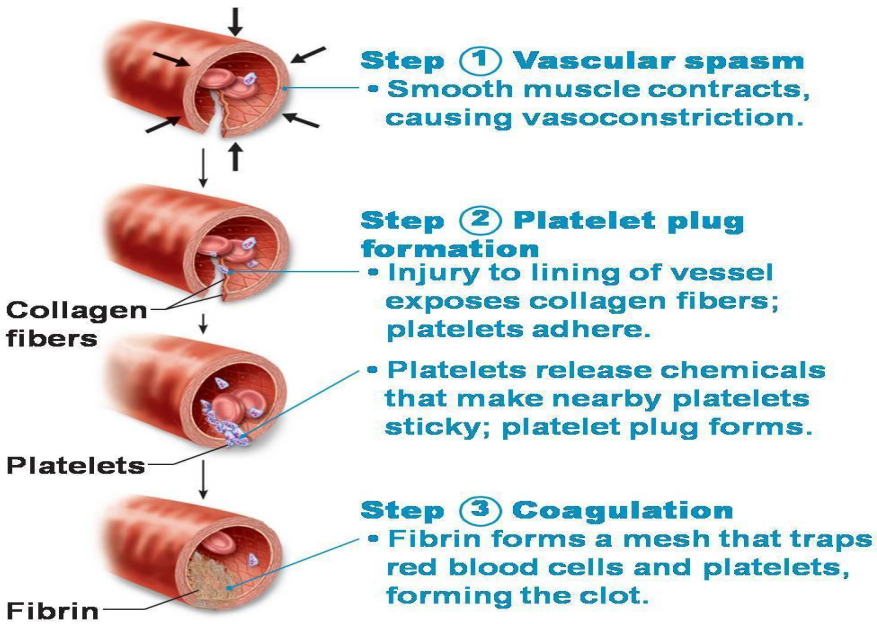
1. **Endothelium Injury**
2. **Platelet**
3. **Von Willebrand Factor**

Responsible for initial formation of platelet plug it's affected in case of: Thrombocytopenia, von willebrand disease and also in platelet function disorder

Secondary Hemostasis:

1. **Clotting Factors**
2. **Soluble Protein Fibrinogen converted to insoluble Fibrin**





BLEEDING DISORDERS

LABORATORY EVALUATION
(to know the source of bleeding)

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

Taking Hx
Congenital:
- Family Hx
- Since Childhood (hemophilia & clotting factors)

Acquired:
- Middle age onset
- Cause leading to DIC

BLEEDING TIME:

PROVIDES ASSESSMENT OF PLATELET COUNT AND FUNCTION

NORMAL VALUE 2-8 MINUTES

PROTHROMBIN TIME (PT):

Measures Effectiveness of the **Extrinsic** Pathway

NORMAL VALUE 10-15 SECS

Prothrombin time tests the extrinsic and final common pathways
Prolongation in:

- Liver disease
- vitamin K antagonism (i.e. warfarin) and deficiency (In Bariatric surgery or removal of stomach)
- Disseminated intravascular coagulation (In severe infection or malignancy)
- Factor VII, X, V, II and fibrinogen defect

PARTIAL THROMBOPLASTIN TIME

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

Q) Pt on Heparin, what is followed is prolongation of PTT

THROMBIN TIME

Not always available, and need accuracy

- Time for Thrombin To Convert Fibrinogen to Fibrin
- A Measure of **Fibrinolytic** Pathway

NORMAL VALUE 9-13 SECS

Thrombin time evaluate fibrinogen and for inhibition of thrombin action

Prolongation in:

- Hypofibrinogenaemia
- Dysfibrinogenaemia (http://www.fmshk.com.hk/hkabth)
- 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.

CONGENITAL BLEEDING DISORDERS

Hemophilia

an inherited bleeding disorder caused by deficiency of coagulation.

- *Hemophilia **A*** – Inherited deficiency of factor VIII (**8**); an **X-linked** recessive disorder. 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).

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)

- *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).

Congenital >> 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, or the presence of other genetic abnormalities (Turner Syndrome or X autosomal translocations).

Acquired >> development of autoantibodies most commonly directed against FVIII – ass. with pregnancy, malignancy, advanced age.

Clinically >> hematomas, **hemarthroses**, bruising, bleeding (mucosal, GI, GU)
Dx >> **aPTT** will be prolonged, **Factor** level will be low, Mixing study (corrected), **Normal VWF & PT** (the most accurate test is a specific assay for factor VIII or IX)
Rx >> 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)

According to the severity of hemophilia the treatment will differ:

- Sever: Prophylaxis is needed
- Mild: Give treatment if the pt bleeds, no need for prophylaxis

Von Willebrand Disease

The most common bleeding disorder.

Defect of Von Willebrand Factor:

- Quantitative (type 1 & 3)
- Qualitative (type 2)

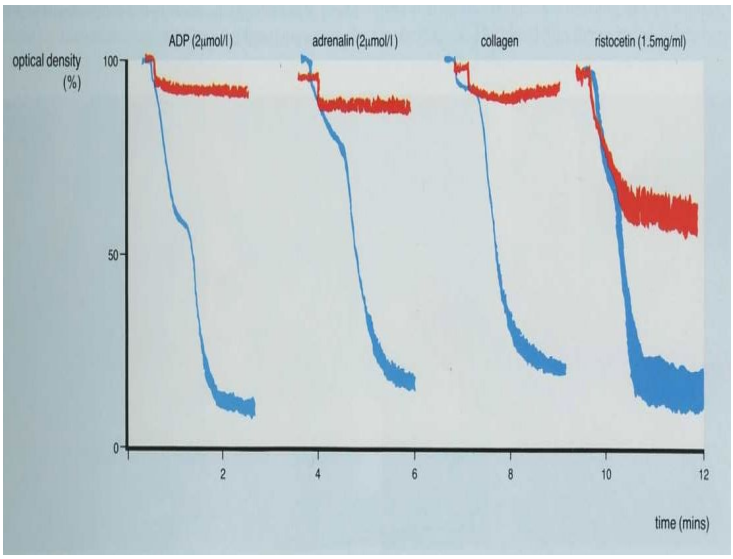
Autosomal dominant (Important in MCQ)
The Normal function of VWF:

- Mediate platelet adhesion
- Stabilize factor VIII in circulation
- Localize factor VIII to site of vessel injury

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

Platelet aggregometry: testing for platelet dysfunction



- control
- thrombasthenia

To distinguish you need VW antigen activity if its diminished with factor 8 diagnostic

To confirm test for platelet ristocetin activity

In case of VWF disease all will be normal ~~except~~ ristocetin

Von Willebrand Disease

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)

Dx >> 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 (low in 2M)

Rx >> Replacement of exogenous vWF concentrate, Desmopressin (DDAVP intranasal) Antifibrinolytic agents (Tranexamic Acid, Aminocaproic Acid), Conjugated Estrogens & oral contraceptive Agents (for menorrhagia)
(best initial therapy is desmopressin if there is no response use factor VIII replacement or vWF concentrate)

Comparison between haemophilia and vWD

	Hemophilia A	Factor IX deficiency	Von Willebrand disease
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

Platelets Disorders

PLATELET COUNT

- 100,000 - 400,000 CELLS/MM3 (NORMAL)
- < 100,000 (Thrombocytopenia)
  - 50,000 - 100,000 (Mild Thrombocytopenia) (No need to give platelets, just follow up)
  - < 50,000 (Severe Thrombocytopenia) (Need intervention)

Plt Disorders (Quantitative)

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
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)
Rheumatologic/autoimmune disorders (eg, systemic lupus erythematosis, rheumatoid arthritis)
Pregnancy
Gestational thrombocytopenia
Preeclampsia
HELLP syndrome (hemolysis, elevated liver function tests, low platelets)

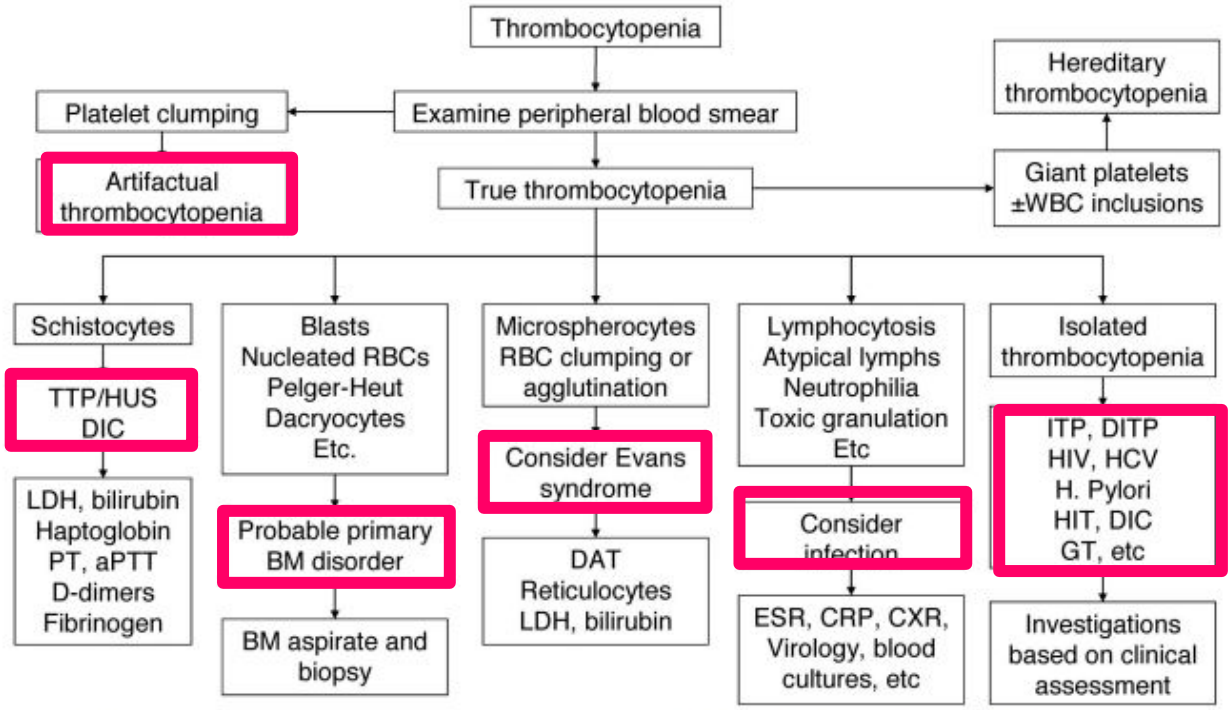
IMP

Portal HTN Cause back pressure on the spleen and increase spleen size, this will lead to decrease in All the cells including platelets so the pt if he develop esophageal varices on top of thrombocytopenia it will lend to severe bleeding

This is the extrahepatic manifestation of Hepatitis:
- one of them is thrombocytopenia
- the other is EVAN Syndrome

Evan syndrome:
- Autoimmune hemolytic cement
- Autoimmune thrombocytopenia

Approach to Thrombocytopenia



Immune Thrombocytopenic Purpura (ITP)

Primary : isolated thrombocytopenia due to immune Plt destruction & reduce production (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

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

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

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

Immune Thrombocytopenic Purpura (ITP) Treatment

Very Important

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, shock, infection, malignancy (esp **APML***), Obstetric complications.

* **IMP in MCQs** (acute promyelocytic leukemia)

Pathogenesis :

massive activation of coagulation that overwhelms control mechanisms thrombosis

Acute consumption of coagulation factors & Plts bleeding

Dx >> Prolonged PT and aPTT, decreased fibrinogen, low plt, high LDH, low haptoglobin

Rx >> treat underlying process, FFP, Cryoprecipitate (Goal Fibrinogen > 100 mg/dL), PLT Tx

Q/ Which type of leukemia is common to have DIC?
A/ APML

Plt Disorders (Qualitative)

ACQUIRED PLT FUNCTIONAL DISORDERS

1. Liver Disease
2. Cardiopulmonary Bypass
3. **Uremia** (CKD)
4. Dysproteinemia (Multiple Myeloma or Waldenstrom Macroglobulinemia)
5. Myeloproliferative Disorders (MPDs)
6. Diabetes Mellitus
7. Acquired Glanzmann thrombasthenia

INHERITED DISORDERS OF PLT FUNCTION

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. Wiskott-Aldrich syndrome
3. Storage Pool Disorders such as Hermansky Pudlak Syndrome (HPS) (Hx of sore throat+Purpura+Arthritis+Abdominal Pain+Nephropathy) (Deficiency of Dense Granules)
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:
I. Detailed Pt & Family Medical History (Crucial & Vital regardless of the prior Lab testing)
II. Laboratory Testing

I. **Detailed Pt & Family Medical History** (Crucial & Vital regardless of the prior Lab testing)
establish likelihood of a bleeding disorder
guide laboratory Testing

- Early in the newborn period (**circumcision**)
- 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)**

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

- 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

Anticoagulants

Direct Thrombin 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

Indirect Thrombin Inhibitors
-aprin

Unfractionated Heparin (UFH)	…… ……..	
LMWH - Enoxaparin	Clexan	4.5 – 7 hr
LMWH - Tinzaparin	Innohep	3 – 4 hr
LMWH - Deltaparin		
Fondaparinux	Arixtra	17 – 21 hr

Vitamin K epoxide reductase Inhibitor

Warfarin	Coumadin	7 – 11 hr

Direct Xa Inhibitors
-xaban

Rivaroxaban	Xarelto	5 – 13 hr
Apixaban	Eliquis	5 – 13 hr
Endoxaban	Savaysa	10 – 14 hr

Antiplatelets

Prostaglandin/COX Inhibitors

Generic Name	Trade Name	Half Life
Aspirin	…… …….	24 – 72 hr

Glycoprotein IIb/IIIa Inhibitors

Abciximab	Reopro	72 hr
Eptifibatide	Integrilin	4 hr
Tirofiban	Aggrastat	4 hr

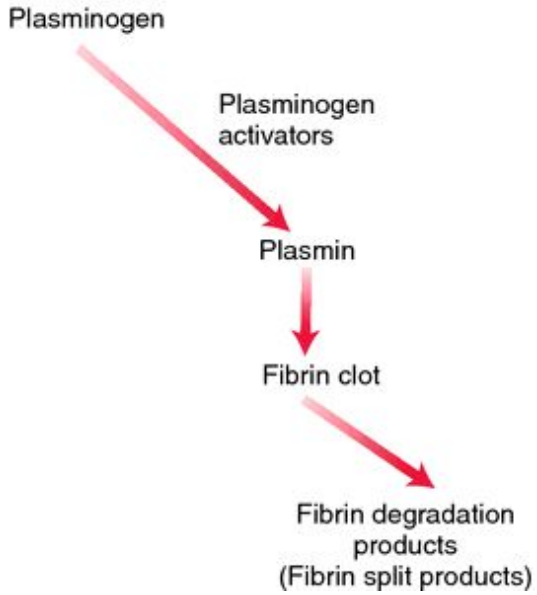
$P2Y_{12}$ ADP Inhibitors

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
	Tenecteplase
Streptokinase (SK)	
Urikinase (UK)	



II. Laboratory Testing

Screening Tests

I. CBC (Platelet count)
II. Prothrombin Time (PT) >> measures F VII, X, V, II, I - (N Time 10-14 secs)
III. International Nmalized 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. $INR = \left(\frac{PT_{test}}{PT_{normal}}\right)^{ISI}$
IV. Activated Partial Thromboplastin Time (aPTT or PTT) >> measures F XII, XI, IX, VIII, X, V, II, I - (N Time 30 – 40 secs)
V. Thrombin (Clotting) Time (TT) >> sensitive to deficiency of Fibrinogen or inhibition of thrombin - (N Time 14 – 16 secs)
VI. Bleeding Time >> (3-8 secs) (not sensitive – not specific)

- Screening tests (not sensitive to all abnormalities ass. w a bleeding disorder)

Causes of Prolonged Coagulation Profile

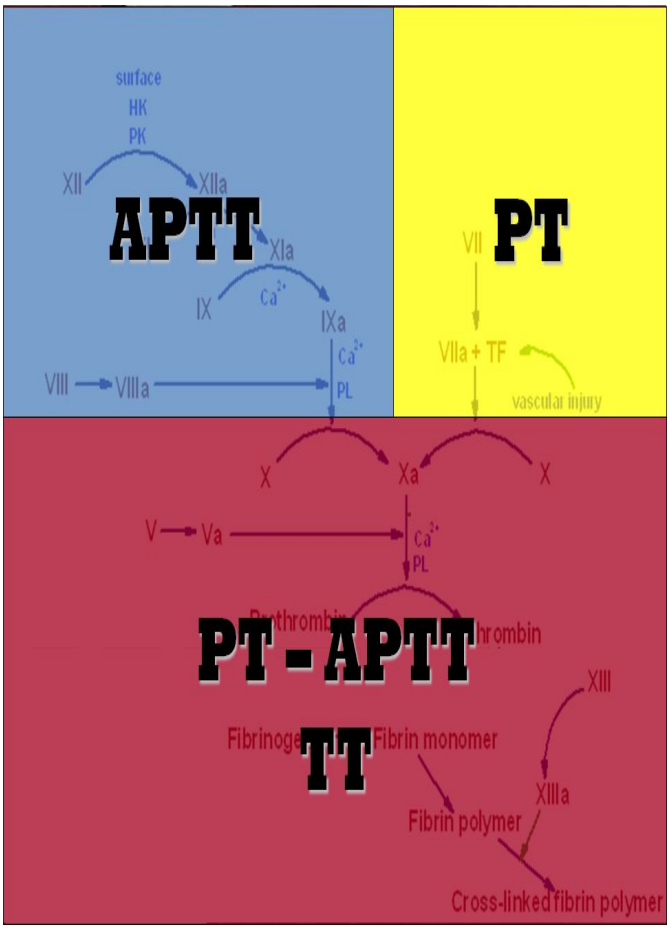
Important MCQs Qs

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

Three patterns:
- Extrinsic pathway
- Intrinsic pathway
- Common Pathway (both tests prolonged)



Specialized Tests

Mixing Study (one to one mix of Pt's plasma & known normal standard plasma, only if PT of aPTT prolonged)

- **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
   a. *Specificity* □ 90 % for severe PLT dysfunction of vWD (vWF plasma levels < 25%)
   b. *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)
5. Human Plasminogen Activator Inhibitor (PAI-1)
6. Alpha 2 AntiPlasmin Inhibitor (α2 AP)

Take Home Message

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

Recommended Books by the doctor

- Essential Hematology (A. V. Hoffbrand, P. A. H. Moss)
- Uptodate
- Oxford Handbook of clinical hematology.

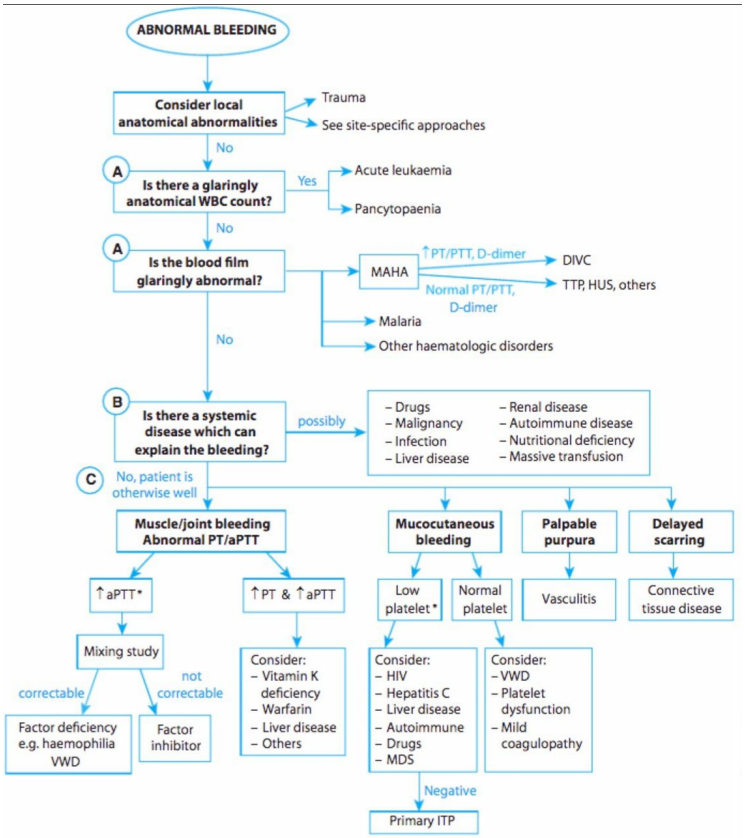
There are extra slides from the doctor that can be found on this link

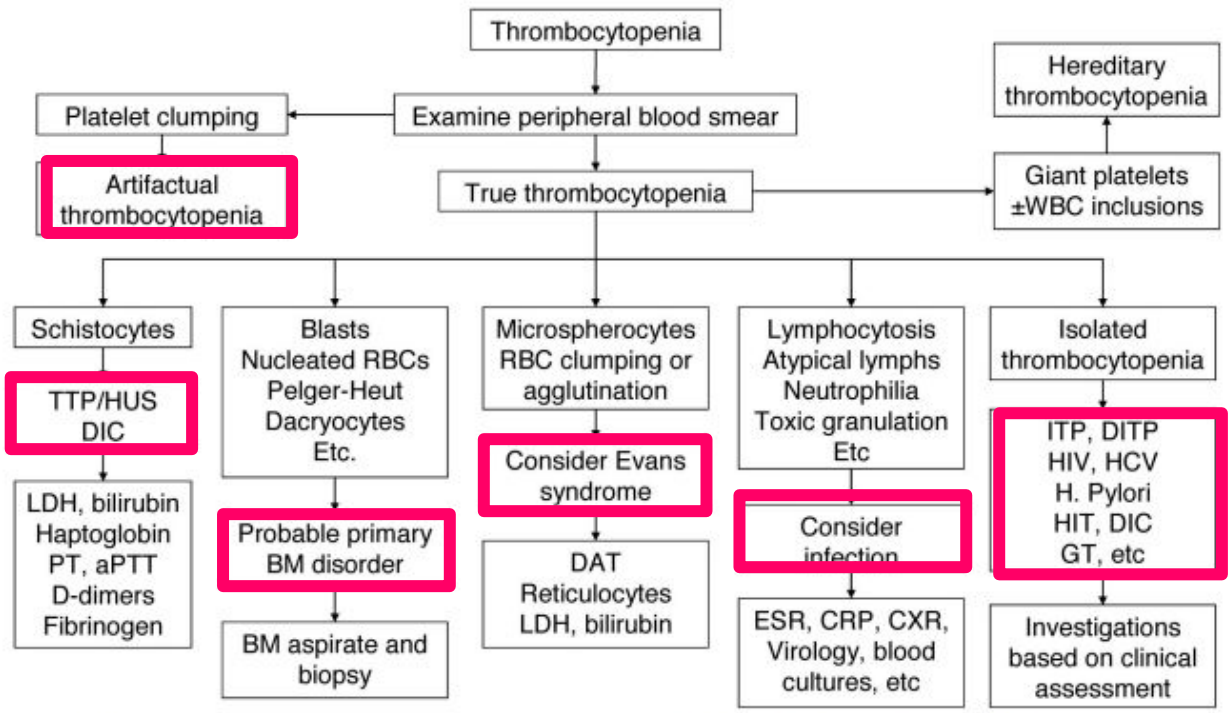
Summary

We recommend this approach when reading the question

Common causes of thrombocytopenia	
Decreased platelet production	• Viral infections (eg, Epstein-Barr virus, hepatitis C, HIV) • Chemotherapy • Myelodysplasia (especially for age >60) • Alcohol use • Congenital (eg, Fanconi syndrome) • Vitamin B12 or folate deficiency
Increased platelet destruction	• Systemic lupus erythematosus • Medications (eg, heparin) • Idiopathic thrombocytopenic purpura, disseminated intravascular coagulation, thrombotic thrombocytopenic purpura-hemolytic uremic syndrome • Antiphospholipid syndrome
Other	• Dilutional due to massive red blood cell transfusion • Splenic sequestration

vancomycin





Summary

Hemophilia		
A	B Christmas Disease	C (ashkenazi jews) Rosenthal Syndrome
8	9	11
X linked recessive		autosomal recessive
Severity and conformation assessed by Factor Levels: Severe less than 1% Moderate 1-5% Mild 5-40%		

Von Willebrand Disease	
Etiology	Qual or Quan, Autosomal dominant (except type 3)
Clinical	-Mostly asymptomatic -Ecchymosis,Petechiae -Other symptoms include epistaxis, gingival bleeding, menorrhagia , GI bleeding, and excessive bleeding during surgical procedures.
Lab	-aPTT :normal (in Type 1 & 2) and prolonged (in Type 2N, 2B, & 3) -Factor 8 will be low in type 2N & 3 -Quantitative assessment by vWF antigen assay: ↓ factor levels -Qualitative assessment by a ristocetin cofactor activity assay Failure of aggregation with a ristocetin assay or a ristocetin cofactor level < 30 IU/dL is considered definitive for vWD
Rx	Recombinant von Willebrand factor (rVWF) concentrate,Desmopressin

Immune thrombocytopenia	
Clinical	-Antecedent Viral infection -Asymptomatic petechiae and ecchymosis -Nasal,GI,GU bleed
Lab	Diagnosis of exclusion -Isolated thrombocytopenia -Peripheral smear: megakaryocyte
Rx	if PLT > 50.000 and no bleeding: observe Other than that: 1st -Steroids, IVIG 2nd -Splenectomy Refractory- TPO agonists (Romiplostim, Eltrombopag)

DIC	
Etiology	Sepsis (most common),Trauma,malignancy(**APML)** ,Obstetric complications
Clinical	-Bleeding + thrombosis
Lab	- ↑PT, ↑aPTT, ↓ Fibrinogen (may be N b/c acute phase) **-+ve D-Dimer**/FDP -↓ PLT -+ve Schistocytes, ↑ LDH, ↓ Haptoglobin
Rx	treat underlying process, FFP, Cryoprecipitate (Goal Fibrinogen > 100 mg/dL), PLT Tx

Questions

A 3-year-old boy is brought to the emergency department because of pain and swelling of his right knee joint for 1 day. He has not had any trauma to the knee. He was born at term and has been healthy since. His maternal uncle has a history of a bleeding disorder. His temperature is 37.1°C (98.8°F) and pulse is 97/min. The right knee is erythematous, swollen, and tender; range of motion is limited. No other joints are affected. An x-ray of the knee shows an effusion but no structural abnormalities of the joint. Arthrocentesis is done. The synovial fluid is bloody. Further evaluation of this patient is most likely to show which of the following?

A. Low platelets
B. Prolonged Partial thromboplastin time
C. Prolonged Prothrombin time
D. Elevated ESR
E. Synovial fluid Leukocytosis

Answer B

A 78-year-old man is brought to the emergency department because of a 1-day history of painful enlarging bruises and skin ulceration over his thighs and external genitalia. He has type 2 diabetes mellitus, mitral regurgitation, and atrial fibrillation. Three days ago, he was started on treatment with warfarin. His only other medications are metformin and lisinopril. His temperature is 37.8°C (100.0°F), pulse is 108/min and irregularly irregular, and blood pressure is 155/89 mm Hg. Examination of the skin shows large purpura, hemorrhagic bullae, and areas of skin necrosis over his anterior legs, gluteal region, and penis. This patient is most likely to benefit from treatment with which of the following?

A. Argatroban
B. Tranexamic acid
C. Protein C concentrate
D. Hyperbaric oxygen

Answer C

A 14-year-old girl is brought to the physician by her mother for the evaluation of recurrent episodes of nose bleeding for several months. The episodes occur unexpectedly and stop after a few minutes by elevating the upper body and bending the head forward. Menses occur at regular 27-day intervals with heavy flow. Her last menstrual period was 3 weeks ago. Vital signs are within normal limits. Physical examination shows no abnormalities. Laboratory studies show:

Hemoglobin	11 g/dL
Hematocrit	34%
Leukocyte count	7,000/mm^3
Platelet count	180,000/mm^3
Prothrombin time	13 sec
Partial thromboplastin time	45 sec
Fibrin split products	negative

The bleeding time is 10 minutes. Which of the following is the most appropriate next step in treatment?

A. Vitamin K
B. Plasma exchange
C. Intravenous Immunoglobulins
D. Desmopressin
E. Factor 8 Substitution

Answer D

A 16-year-old girl is brought to the physician because of a 6-month history of menstrual cramps, heavy menstrual flow, and fatigue; she has gained 5 kg (11 lb) during this period. Menses occur at regular 30-day intervals and last 8 to 10 days; during her period she uses 7 tampons a day and is unable to participate in any physical activities because of cramping. Previously, since menarche at the age of 11 years, menses had lasted 4 to 5 days with moderate flow. Her last menstrual period was 3 weeks ago. She has limited scleroderma with episodic pallor of the fingertips. She takes no medications. She is 160 cm (5 ft 3 in) tall and weighs 77 kg (170 lb); BMI is 30 kg/m^2. Her temperature is 36.5°C (97.7°F), pulse is 56/min, respirations are 16/min, and blood pressure is 100/65 mm Hg. Physical examination shows a puffy face with telangiectasias and thinning of the eyebrows. Deep tendon reflexes are 1+ bilaterally with delayed relaxation. Pelvic examination shows a normal appearing vagina, cervix, uterus, and adnexa. Further evaluation of this patient is most likely to show which of the following findings?

A. Prolonged aPTT
B. Prolonged PT
C. Decreased level of vW Factor
D. High TSH

Answer is D (not just because it's all heavy menstrual periods are Bleeding disorder be careful in the exam)