433 Teams

MEDICINE

12|Bleeding Disorders

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COLOR INDEX

Slides - Step-Up medicine - Kaplan Notes - Extre explanation - Doctor Notes

Objectives: not given

First few slides will talk about normal physiology then later will talk about the disorders.

Hemostasis

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

- Cellular Components: (PLTs& Endothelium)
- Plasma Proteins Components: 3 protein systems

1. Blood Coagulation (Clot Formation)
2. Fibrinolysis (Clot Lysing)
3. Anticoagulant (Regulating)

#PLATELETS (PLTs):

- Produced in the Bone Marrow by fragmentation of the cytoplasm of megakaryocytes.
- Each megakaryocyte gives from 1000 to 5000 platelets.
- Thrombopoietin: the major regulator of Plt production (produced by Liver & Kidney)
- Normal PLT count is(150 – 400 x 10^9)
- PLT Life Span is (7 – 10 days)

3 types of storage granules in platelets

- ***α Granules***
  - Clotting Factors
  - **VWF**
  - PDGF
  - ILGF1
- ***Dense Granules (δ Granules)***
  - ADP & ATP
  - Serotonin
  - Histamine
  - Ionized Ca
- ***Lysosomes***
  - Hydrolytic enzymes

PLTs Receptors

Table 1 Platelet receptors

Receptors	Ligands
Initiation phase (adhesion)	
GPIb-IX-V complex	VWF
Extension phase (activation)	
GPVI	Collagen
GPIa/IIa (a2β1, VLA-2 or CD49b/CD29)	Collagen
GPCRs	ADP and thromboxane A2, epinephrine and thrombin
P2Y1, P2Y12	ADP
PAR-1 and PAR-4	thrombin
Stabilization phase (aggregation)	
GPIIb-IIIa (aIIbβ3)	Fibrinogen, VWF
P-selectin	PSGL-1
Receptors with no clear function in hemostasis	
CLEC-2	Podoplanin
FcγRIIA	Collagen

ADP, adenosine diphosphate; VWF, von Willebrand factor; CLEC-2, C-type lectin-like receptor 2; GP, glycoprotein; GPCRs, G protein-coupled receptors; P2, purinoceptor 2 receptor; PAR, protease activated receptor.

PLTs Function

I. Adhesion of plts to vessel wall ☚ VWF binds to GP Ib/IX/V receptor (VWF is 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.

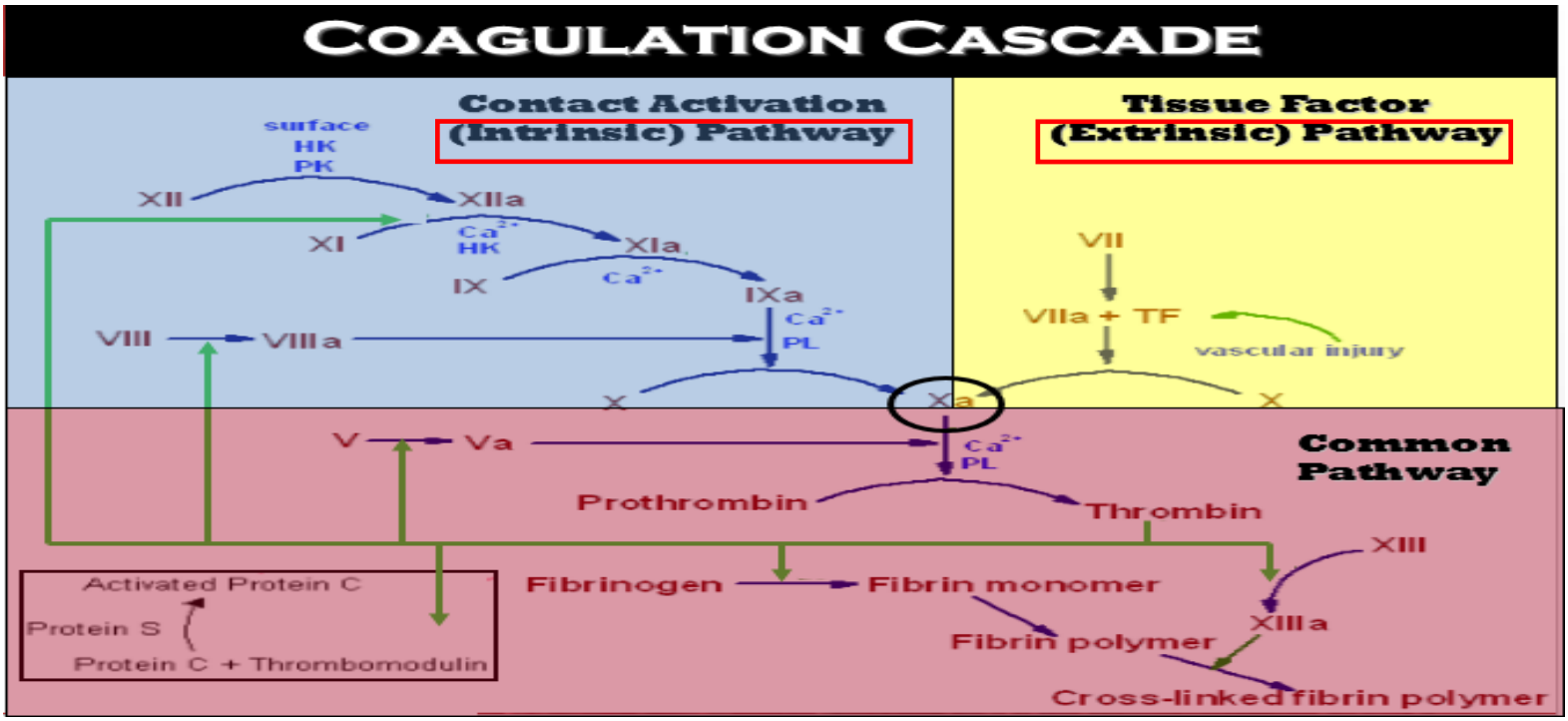
#Clotting Factors:

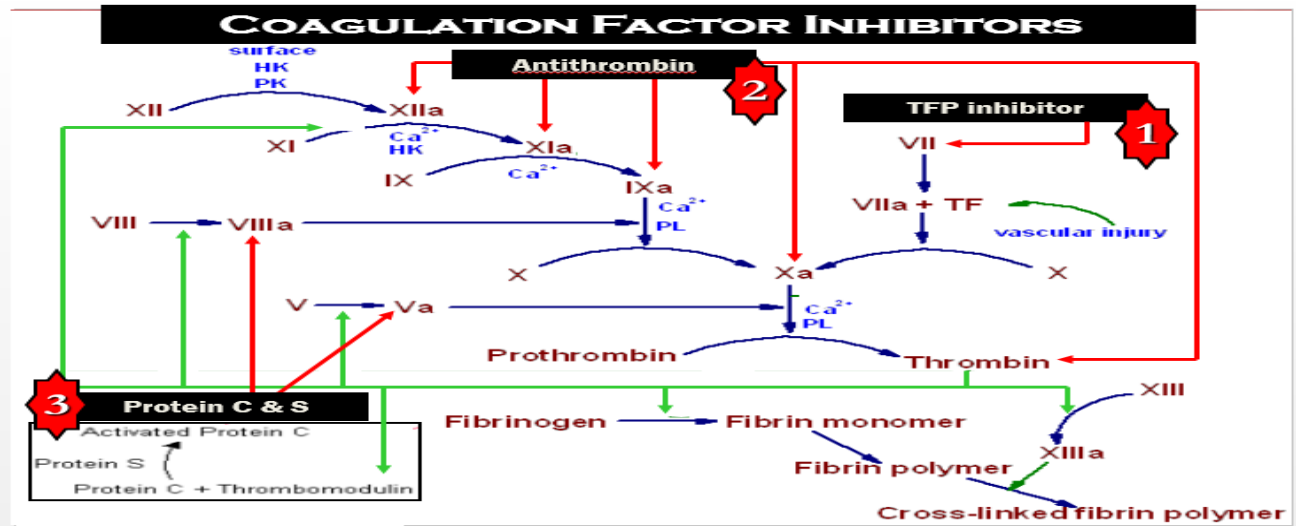
Clotting Factors in Blood and Their Synonyms

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	

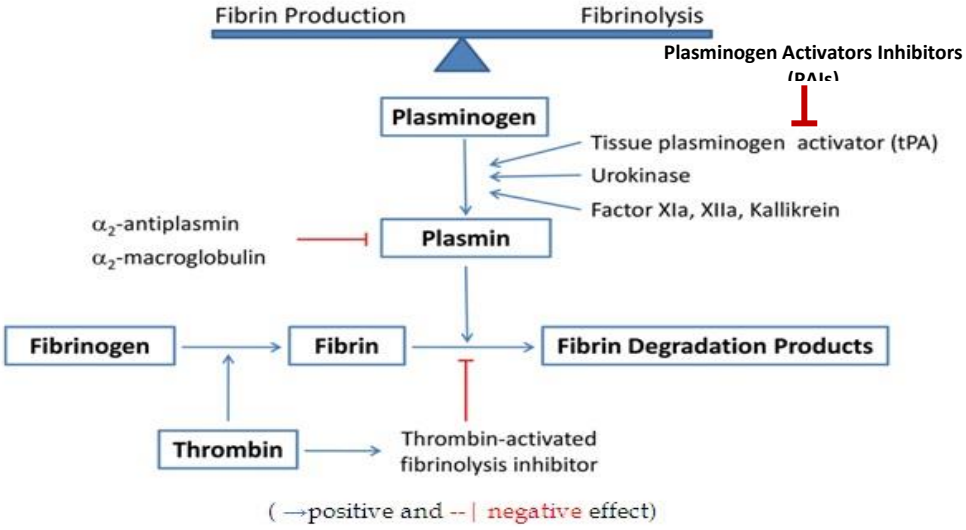
PLT Function Inhibitors

- **Prostacyclin (PGI_2);**
  Synthesized by vascular endothelial cells ☛
  Potent inhibitor of PLT aggregation & causes vasodilation
- **Nitric Oxide (NO);**
  Released from endothelial cells, macrophages, & Plt ☛
  Inhibits Plt activation & promotes vasodilatation





#Fibrinolysis :



#Hemostatic Phases:

I. **Vascular Phase:** Release of locally active vasoactive agents (Endothelin, ThromboxaneA2,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.**

- Defects of Primary Hemostasis (PLT or VW Factor) would lead to :

Mucocutaneous Bleeding

- **Easy bruising**
- **Epistaxis**
- **Menorrhagia**

Secondary Hemostasis:

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

- Defects of Secondary Hemostasis (Clotting Factors Deficiencies) would lead to:

Deep Tissue Bleeding

- ***Joints***
- ***Muscles***
- ***Central Nervous System***

#Approach to Patients with Potential Bleeding:

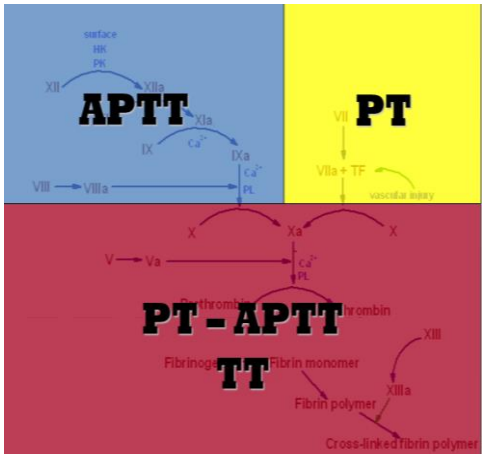
A) Establishing likelihood (suspicion) of bleeding disorder:

- Early in the newborn period (circumcision)
- After hemostatic Challenges (delivery, trauma, surgery, invasive dental procedure,menstruation)
- Frequency & pattern
- Duration : onset (congenital vs. acquired)& time required for cessation
- Sites of bleeding (specific or multiple)
- Current use of medications or herbal supplements

-Clinical Manifestation of Bleeding Disorders: (how to differentiate between primary and secondary hemostasis defects clinically)

Bleeding symptoms	Bleeding disorder	
	Platelet defects (qualitative or quantitative)	Clotting factor deficiencies (eg, factor VIII or factor IX deficiencies)
Overview of bleeding events	**Mucocutaneous bleeding (oral cavity, nasal, gastrointestinal, and genitourinary sites)**	**Deep tissue bleeding (including joints and muscles)**
Excessive bleeding after minor cuts	Yes	Not usually
Petechiae	Common	Uncommon
Ecchymoses	Generally small and superficial; may be significant, depending upon the defect or degree of thrombocytopenia	May develop large subcutaneous and soft tissue hematomas
Hemarthroses, muscle hematomas	Uncommon	Common in severe deficiency states or in association with injury in those with mild to moderate deficiency states
Bleeding with invasive procedures, including surgery	Often immediate, with degree of bleeding dependent upon the severity of the defect, ranging from none (eg, mild degrees of thrombocytopenia or mild platelet function defect) to mild to severe (eg, Glanzmann thrombasthenia)	May be associated either with procedural bleeding or delayed bleeding, depending upon the type and severity of the defect

B) Laboratory Testing:



Screening Tests:

- CBC (Platelet count)
- Prothrombin Time (PT): extrinsic pathway
- measures F VII, X, V, II, I - (Normal Time 12-16 secs)
- International Nmalized Ratio (INR) it's PT when used

  to measure oral anticoagulants is expressed as the international normalized ratio, INR
- Activated Partial Thromboplastin Time (aPTT or PTT): intrinsic pathway
  measures F XII, XI, IX, VIII, X, V, II, I - (Normal Time 26 – 37 secs)
- Thrombin (Clotting) Time (TT) : sensitive to deficiency of Fibrinogen or inhibition of thrombin - (Normal Time 12-14 secs)

Specific Tests:

- Mixing Study or Correction test "important" (Done if PT and/oraPTT prolonged. It is done by mixing the patient's plasma with another normal standard plasma). The result will be either:
  A. Corrected (PT andaPTT become normal): this means there is a clotting factor deficiency.
  B. Not corrected (PT and aPTT still prolonged): this means there are inhibitors (these inhibitors directed against specific factor or global inhibitors " Lupus Inhibitor, risk of thrombosis ")
- PLT Function Assay (PFA - 100): assess PLT function
  Specificity ☛ 90 % Sensitivity ☛ 24 – 41 % (low)
- PLT Aggregation Tests:(5 external aggregating factors; ADP, Collagen, Ristocetin, Arachidonic Acid, Adrenaline)
- Factor XIII assay(F XIII Deficiency >> normal PT & PTT) **(the only factor deficiency NOT cause prolonged PT or aPTT is factor XIII deficiency)**

Note: 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 the extent of the laboratory investigations.

#Congenital Bleeding Disorders

1) Hemophilia: (the most common **inherited bleeding disorders**)

A bleeding disorder caused by deficiency of coagulation factors.

There are three types:

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

2-***Hemophilia B*** – Inherited deficiency of factor IX (9); also called Christmas Disease; an X-linked recessive disorder.

3-***Hemophilia C*** – Inherited deficiency of factor XI (11); also called Rosenthal Syndrome; an autosomal recessive disorder. Rarely, heterozygotes may have bleeding. Common in Ashkenazi Jews.

The severity and the degree of bleeding Symptoms correlate with Factor levels:

Degree of symptoms	Factor level
Severe Hemophilia	**<1 % factor activity (<0.01 IU/mL)**
Moderate Hemophilia	**≥1-5 % of normal factor activity(≥0.01-0.05 IU/mL).**
Mild Hemophilia	**≥5 % to<40 % of normal factor activity (≥0.05 - <0.40 IU/mL).**

Although it is known that hemophilia is inherited, rarely it could be acquired.

Congenital: genetic mutation in F8 & F9 located on the long arm of X chromosome.

- Observed commonly in males due to their hemizygous state
- Extremely Rare in females. (very rarely affect 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: rare but potentially life-threatening bleeding disorder caused by the development of autoantibodies (inhibitors) directed against plasma coagulation factors, most frequently factor VIII (FVIII). Associated with pregnancy, malignancy, advanced age.

Symptoms and signs:hematomas, hemarthroses, bruising, bleeding (mucosal, GI, GU)

Investigations and diagnosis:

- Prolonged aPTT
- low Factor Level (F VIII or FIX or F XI)
- Mixing study (corrected)
- 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 Factor VIIa (with inhibitors)

2) Von Willebrand Disease: (The most common bleeding disorder)

Congenital: autosomal dominant (most types), recessive (rarely)

Acquired: is a rare bleeding disorder that might be caused by other medical problems or medicines. It prevents blood from clotting properly.

Caused by autoantibodies against VWF. Treatment in this type will be directed to the underlying disorder.

Examples of medical problems that might cause acquired Von Willebrand's disease: Solid tumors, SLE, bone marrow disorders, hypothyroidism, aortic stenosis

Types:

	VWD Types	Defect	Multimers
partial quantitative	Type 1	No mutations – Partial deficiency	Normal Distribution (decrease in quantity)
qualitative	Type 2A	Decrease vWF-dependent PLT adhesion with selective deficiency of HMWM which required for normal PLT adhesion	Absence of large & medium MW multimers
	Type 2B	Increase Affinity to PLT GPIb (gain of function mutations) ☛ low PLT, ↑ LD-RIBA	Absence of large MW multimers
	Type 2M	Decrease vWF-dependent PLT adhesion without selective deficiency of HMWM ☛ Decrease Affinity to PLT GPIb (loss of function mutations)	Normal distribution (decrease in quantity)
	Type 2N	Decrease Affinity to FVIII ☛ low FVIII	Normal distribution
complete quantitative	Type 3	Variety of mutations & large deletions – Complete deficiency	Absent

Symptoms and signs:

Look for bleeding related to platelets (epistaxis, gingival, gums) with a normal platelet count.

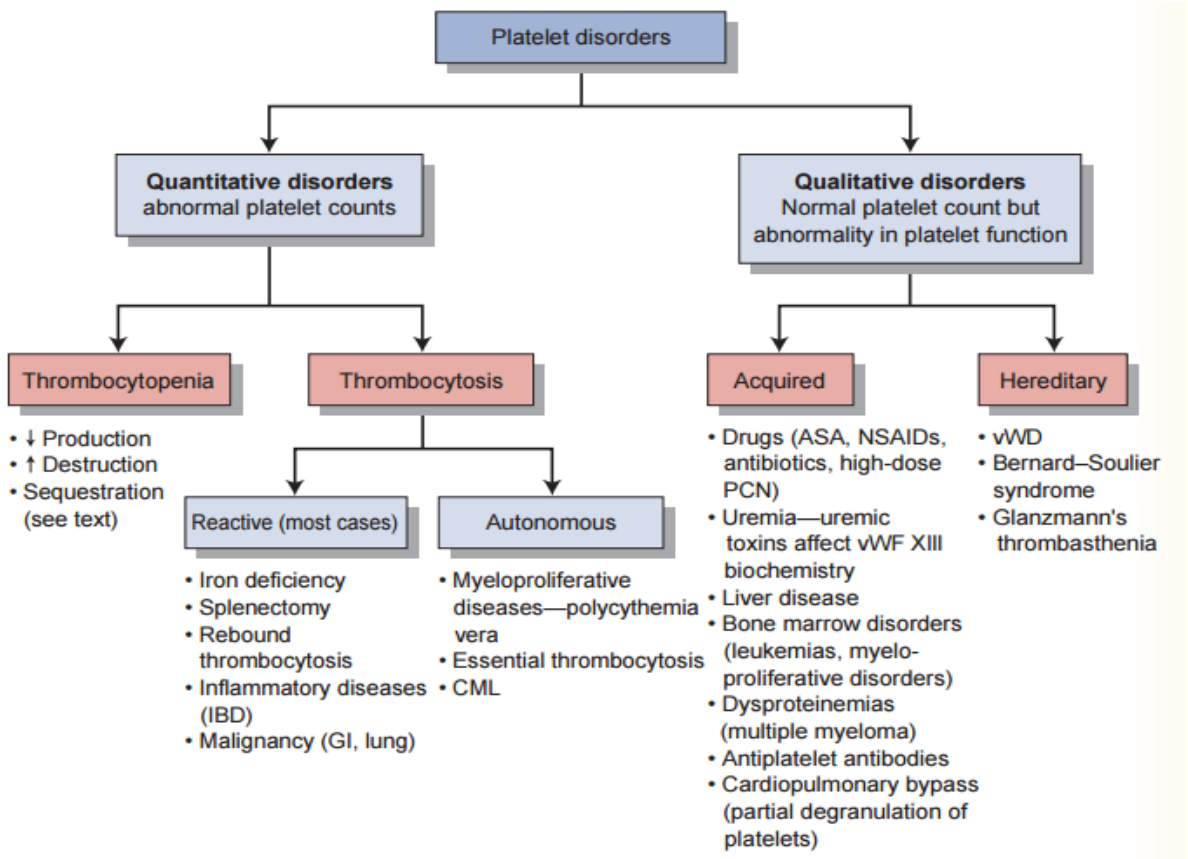
Investigations and diagnosis:

- VWF (antigen) level may be decreased
- Ristocetin cofactor assay: detects VWF dysfunction, also called VWF activity
- Factor VIII activity
- Bleeding time: increased duration of bleeding (rarely done)
- aPTT may be elevated in half of patients

Treatment:

The best initial therapy is DDAVP (desmopressin), which releases subendothelial stores of VWF. If there is no response, use factor VIII replacement or VWF concentrate. In addition, in case the patient has menorrhagia we give oral contraceptive agents.

#Platelets Disorders



Immune Thrombocytopenic Purpura (ITP): "Quantitative"

This results from autoimmune antibody formation against host platelets. These antiplatelet antibodies (IgG) coat and damage platelets, which are then removed by splenic macrophages.

Primary: isolated thrombocytopenia due to immune Platelets destruction &decrease production (auto AB to megakaryocytes)

Secondary: associated with disease/drug exposure ☛ Viral (HIV, HCV, HBV, EBV, CMV, Parvovirus), SLE, APLS,H. Pylori Infection, Chronic Lymphocytic Leukemia (CLL), Hodgkin Lymphoma, AIHA (Autoimmune Hemolytic Anemia).

Symptoms and Signs:

- Petechiae and ecchymoses on the skin.
- Bleeding of the mucous membranes.

Investigations and diagnosis: "Diagnosis of exclusion"

1. The platelet count is frequently less than 20,000. The remainder of the blood count is normal.
2. Peripheral smear shows decreased platelets.
3. Bone marrow aspiration shows increased megakaryocytes.
4. There is an increased amount of platelet-associated IgG.

Treatment:

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

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

Thrombotic Thrombocytopenic Purpura: is a rare blood disorder characterized by clotting in small blood vessels of the body (thromboses), resulting in a low platelet count.

TTP Pentad (five features): 1-thrombocytopenia,

2-microangiopathichaemolyticanaemia (MAHA) (100%), 3-Renal Failure (50%), 4-Neurological symptoms (65%), 5-Fever (25%) ☛ all 5 in only 5 %.

Hemolytic Uremic Syndrome: Hemolytic-uremic syndrome (HUS) is a clinical syndrome characterized by progressive renal failure that is associated with microangiopathic, hemolytic anemia and thrombocytopenia.

HUS Triad: Thrombocytopenia, microangiopathichaemolyticanaemia (MAHA), Renal Failure.

Pathophysiology:

TTP (deficiency in ADAMTS13 proteatse activity or existence of inhibitor ☛ persistence of large vWF multimers on endothelia surface ☛ adhesion & aggregation of passing PLTs ☛ thrombosis)

HUS (Shiga toxins bind & activate renal endothelial

cells & PLTs ☛ intrarenal thrombi)

Causes of TTP:

Familial or idiopathic, or secondary to:

-Drugs (Chemotherapy, Tacorlimus, Gemcitabine, Mitomycin-C, Ticlopidine, Clopidpgrel, Quinine), HIV, Pregnancy, Hematopoietic stem cell transplantation (HSCT), Autoimmune Diseases like SLE

Investigations and diagnosis:

- Thrombocytopenia + MAHA
- +ve Schistocytes (> 2-3/hpf), -ve Coombs
- Normal PT/aPTT & Fibrinogen
- ADAMTS13 Deficiency

Treatment:

- Plasmapheresis (large volume)
- Corticosteroids and splenectomy, may help in some cases
- Eculizumab in HUS
- Platelet transfusion is contraindicated because that Will cause microvascular thrombosis.

Most cases of hemolytic uremic syndrome develop in children after two to 14 days of diarrhea — often bloody — due to infection with a certain strain of Escherichia coli (E. coli). Source: Mayo Clinic

Disseminated Intravascular Coagulation (DIC):

Definition:

DIC is characterized by abnormal activation of the coagulation sequence, leading to formation of microthrombi throughout the microcirculation. This causes consumption of platelets, fibrin, and coagulation factors. Fibrinolytic mechanisms are activated, leading to hemorrhage. Therefore, bleeding and thrombosis occur simultaneously.

Causes:

- Infection: most common cause, especially gram-negative sepsis.
- Obstetric complications: amniotic fluid emboli (often acute and fatal); retained dead fetus (often chronic); abruptio placentae.
- Major tissue injury: trauma, major surgery, burns, fractures.
- Malignancy: acute promyelocytic leukemia e ,lungs, pancreas, prostate, GI tract.
- Shock, circulatory collapse
- Snake venom (rattlesnakes)

Pathogenesis:

- massive activation of coagulation that overwhelms control mechanisms ☛ thrombosis
- Acute consumption of coagulation factors &Plts☛ bleeding

Investigations and diagnosis:

- Elevation in both the PT and aPTT
- Low platelet count
- Elevated d-dimer and fibrin split products
- Decreased fibrinogen level (it has been consumed)

Treatment:

- Treat the underlying cause. If platelets are under 50,000/microleter and the patient has serious bleeding, replace platelets as well as clotting factors by using FFP (Fresh Frozen Plasma). Heparin has no definite benefit. Cryoprecipitate may be effective to replace fibrinogen levels if FFP does not control bleeding.

Heparin-Induced Thrombocytopenia

- Can occur with use of any amount of heparin. Mostly occurs with unfractionated heparin. Low–molecular-weight heparin (LMWH) has a much lower risk of HIT.
- Drop in platelets a few days after heparin administration. Platelets aggregate ("clump") leading to venous thrombosis (deep vein thrombosis [DVT], pulmonary embolism [PE])
- Decrease in platelet count by 50% suggests HIT.
- Diagnostic tests: antiplatelet factor IV antibody or serotonin release assay
- Treatment: stop heparin. If anticoagulation is indicated (venous thrombosis), give a thrombin inhibitor such as lepirudin.
- Avoid heparin in the future in any patient who has developed an episode of HIT.

Bernard–Soulier Syndrome: "Qualitative"

- 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.

Glanzmann'sThrombasthenia: "Qualitative"

- Autosomal recessive disease
- Disorder of platelet aggregation due to deficiency in platelet glycoprotein GPIIb-IIIa
- Bleeding time is prolonged.
- Platelet count is normal.

#Drugs Used for Clotting Disorders

- **Anticoagulants:**
  - ✓ Direct Thrombin Inhibitors like Dabigatran
  - ✓ Indirect Thrombin Inhibitors like Heparin
  - ✓ Vitamin K epoxide reductase Inhibitor like Warfrin
  - ✓ Direct Xa Inhibitors like Rivaroxaban
- **Antiplatelets:**
  - ❖ Prostaglandin/COX Inhibitors like Aspirin
  - ❖ Glycoprotein IIb/IIIa Inhibitors like Abciximab
  - ❖ $P2Y_{12}$ ADP Inhibitors like Clopidogrel
- **Thrombolytics:** Plasminogen Activators like Alteplase

COAGULATION 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.

TABLE 9-5 Laboratory Findings for Bleeding Disorders

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

[a]NL = normal.

MCQs

1-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
e. Cirrhosis with sequestration of erythrocytes and platelets in the spleen

2-. 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

3-. A 73-year-old woman is admitted for deep venous thrombosis and concern for pulmonary embolism. She has a history of type 2 diabetes mellitus, hypertension, and coronary artery disease. She had been admitted for a three-vessel coronary artery bypass graft 2 weeks prior to this admission. She did well and was dismissed 5 days after the procedure. Pain and swelling of the right leg began 2 days before this admission; she has noticed mild dyspnea but no chest pain. The clinical suspicion of deep vein thrombosis (DVT) is confirmed by a venous Doppler, and the patient is started on unfractionated heparin. Her initial laboratory studies, including CBC, are normal. The next day her pain has improved, and helical CT scan of the chest reveals no evidence of pulmonary embolism. She is instructed in the use of low-molecular-weight heparin and warfarin; she is eager to go home. Her serum creatinine is normal. Her predischarge CBC shows no anemia, but the platelet count has dropped to 74,000. An assay for antibodies to heparin-platelet factor 4 complexes is ordered.

What is the best next step in her management?

a. Dismiss the patient on low-molecular heparin, warfarin, and close outpatient follow-up.
b. b. Obtain a liver-spleen scan to look for platelet sequestration.
c. c. Discontinue all forms heparin, continue warfarin, and add aspirin 162 mg daily until INR becomes therapeutic.
d. d. Keep the patient in the hospital, discontinue unfractionated heparin, add low-molecular-weight heparin, and monitor the platelet count daily.
e. e. Keep the patient in the hospital, discontinue all forms of heparin, and start the patient on lepirudin by intravenous infusion.
f.

4-. 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.

e. Restrict dietary vitamin K.

5-. 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. Give vitamin K.

e. Begin red blood cell transfusion

Answers: 1-C 2-C 3-E 4-C 5-B

1-. The answer is c. (Fauci, pp 1813-1815.) This patient has thrombotic thrombocytopenic purpura (TTP). TTP is an acute life-threatening disorder that is characterized by the pentad of microangiopathichemolytic anemia, nonimmune thrombocytopenia, fever, renal insufficiency, and CNS involvement (confusion or multifocal encephalopathy). Not all patients have the full pentad; the essential features are the red blood cell fragmentation (schistocytes and helmet cells) and the thrombocytopenia. TTP may be triggered by endothelial damage and is associated with deficiency of a plasma protein (ADAMTS 13) that breaks down multimers of von Willebrand factor. Plasma exchange (with the infusion of fresh frozen plasma to provide the missing ADAMTS 13 protein) can be lifesaving. The hemolytic uremic syndrome (HUS), often associated with Shigatoxin-producing strains of E coli O157:H7), is similar but is usually not accompanied by CNS changes. The renal failure is usually more severe in HUS. Disseminated intravascular coagulation (DIC) associated with sepsis can resemble TTP, but the coagulation pathway is
usually activated in DIC. In TTP the prothrombin time, PTT, and fibrinogen level are normal. Antiplatelet antibodies are associated with idiopathic thrombocytopenic purpura (ITP), but this patient has multiple abnormalities, not just thrombocytopenia. Hypersplenism can cause thrombocytopenia but rarely with a platelet count of below 50,000; it is not associated with red cell fragmentation

2-. The answer is c. This woman's lifelong history of excessive
bleeding suggests an inherited bleeding problem, as does the positive family history. The prolonged PTT indicates a deficiency of factors VIII, IX, XI, or XII, but the commonest of these deficiencies (classic hemophilia A and Christmas disease, or hemophilia B) are vanishingly rare in women. Furthermore, the continued oozing from dental sites and the absence of ecchymoses or hemarthroses suggest a platelet function disorder, as does the prolonged bleeding time. Von Willebrand disease is an autosomal dominant condition that leads to both platelet and factor VIII dysfunction and is the likeliest diagnosis in this patient. Although factor VIII concentrates can be used for life-threatening bleeding, most will respond to desmopressin, which raises the von Willebrand factor level in the most common form (the so-called type 1 form) of this disease. Mild von Willebrand disease is fairly common (1 in 250 individuals). Fresh frozen plasma and whole blood are much less effective ways to deliver factor VIII. Platelet transfusion would not be as effective as correction of the von Willebrand factor level.

3-. The answer is e. Heparin is the commonest cause of drug-induced
thrombocytopenia. Between 10% and 15% of patients receiving unfractionated heparin develop thrombocytopenia. The drop in platelet count is attributed to the production of an antibody against a complex of heparin and platelet factor 4. Low-molecular-weight heparin can also cause thrombocytopenia, although less frequently than unfractionated heparin. Usually the platelet count drops 5 to 10 days after heparin is started. In this case, however, the patient likely had been exposed to heparin at the time of her CABG. With previous exposure, the thrombocytopenia can begin within hours of the reinstitution of any form of heparin. Although low-molecular-weight heparin causes HIT less frequently than unfractionated heparin, all heparin products must be discontinued in the patient with HIT. In all patients with an active clot and those with HITT (heparin-induced thrombocytopenia with thrombosis), a direct thrombin inhibitor must be started and used as a bridge to full-potency warfarin therapy. The chief consequence of HIT is not bleeding but accelerated clotting resulting from the aggregation of platelet-heparin complexes in the circulation. HITT is a feared complication of HIT. Even with proper treatment, the amputation rate (owing to intra-arterial clotting) is as high as 40%, and the death rate as high as 25%.

4- The answer is c. (Fauci, pp 743-745.) Rifampin induces the cyto-chrome P450 that metabolizes warfarin; higher doses of warfarin are required to overcome this effect. When rifampin is stopped, the dose of warfarin necessary to produce a therapeutic prothrombin time will decrease. Barbiturates also accelerate the metabolism of warfarin. Many drugs interfere with the metabolism and clearance of warfarin. Drugs such as nonsteroidal anti-inflammatories can compete with warfarin for albumin-binding sites and will lead to an increased prothrombin time. The list of medications that can either increase or decrease the effect of warfarin is long; all patients given this drug should be advised to contact their physician before taking any new drug. They should also be counseled about over-the-counter drugs (aspirin and NSAIDs) and even health food supplements (such as ginkgo biloba) which can affect the prothrombin time in these patients. A stable intake of vitamin K–containing foods (ie, green leafy vegetables) is recommended.

5- The answer is b. (Fauci, pp 728-731, 937-938.) This patient with gram-negative bacteremia has developed disseminated intravascular coagulation (DIC), as evidenced by multiple-site bleeding, thrombocytopenia, fragmented red blood cells on peripheral smear, prolonged PT and PTT, and reduced fibrinogen levels from depletion of coagulation proteins. Initial treatment is directed at correcting the underlying disorder—in this case, infection. Although heparin was formerly recommended for the treatment of DIC, it is now used rarely and only in unusual circumstances (such as acute promyelocyticleukemia). For the patient who continues to bleed, supplementation of platelets and clotting factors (with fresh frozen plasma or cryoprecipitate) may help control life-threatening bleeding. Red cell fragmentation and low platelet count can be seen in microangiopathic disorders such as thrombotic thrombocytopenic purpura (TTP), but in these disorders the coagulation pathway is not activated. Therefore, in TTP the prothrombin time, partial thromboplastin time, and plasma fibrinogen levels will be normal. Plasmapheresis, vitamin K therapy, and RBC transfusion will not correct the underlying cause.

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