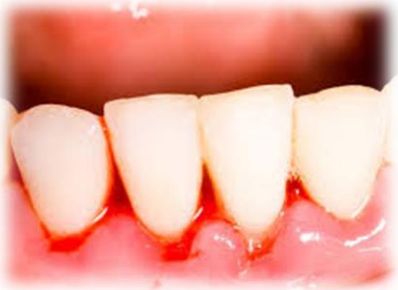

جامعة الملك سعود
King Saud University
1957

BLEEDING DISORDERS

" MADE EASY"

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KING KHALID UNIVERSITY HOSPITAL – KING SAUD UNIVERSITY

OUTLINES

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

Hemostasis

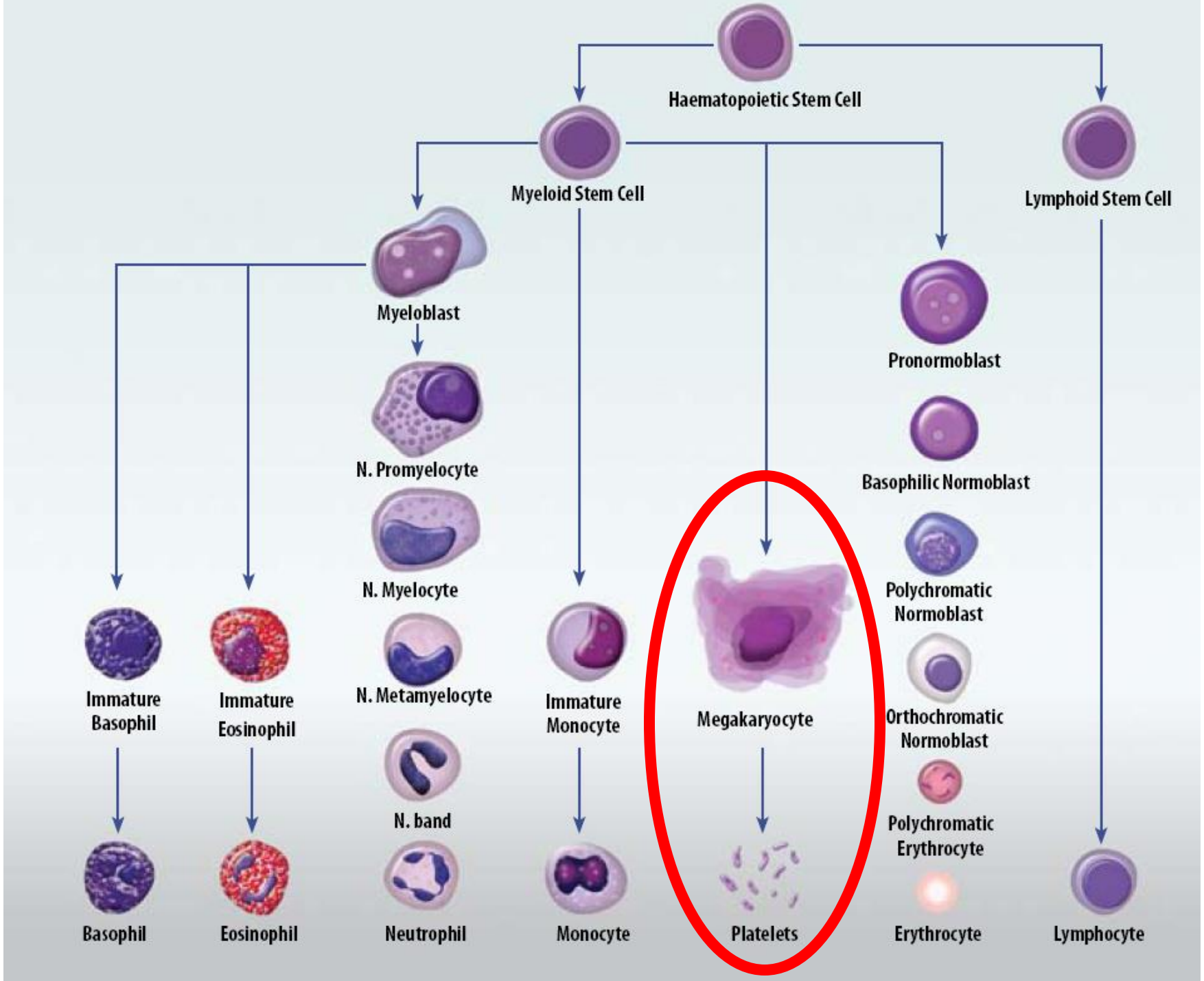
The process through which bleeding is controlled at a site of damaged or disrupted endothelium.

A dynamic interplay between

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

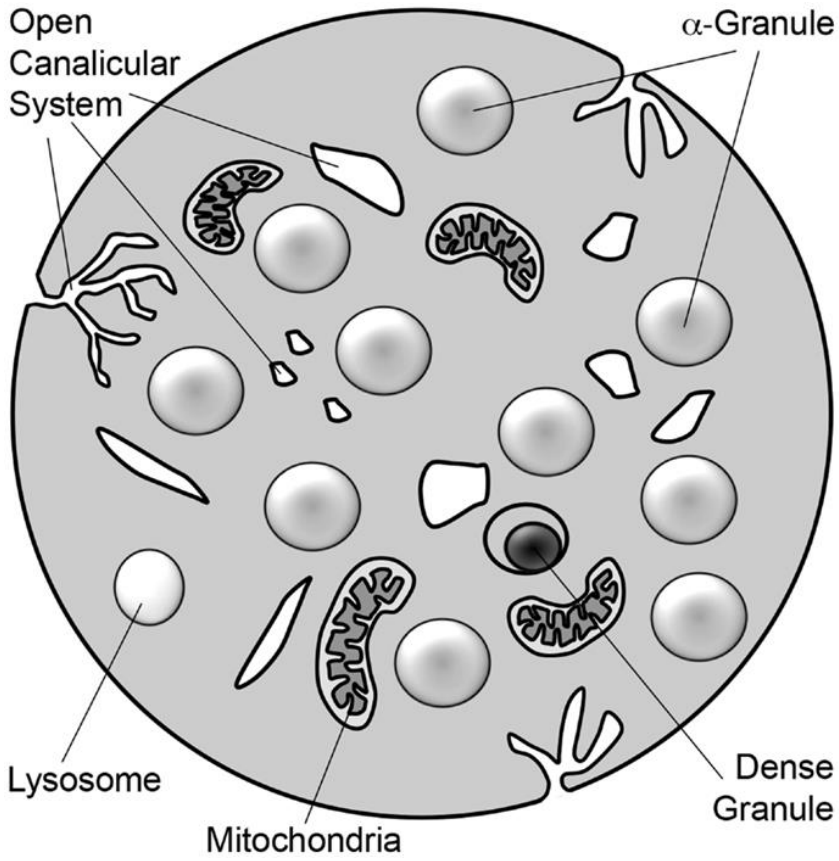
PLATELETS

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


Haematopoietic Stem Cell
Myeloid Stem Cell
Lymphoid Stem Cell
Myeloblast
N. Promyelocyte
N. Myelocyte
N. Metamyelocyte
N. band
Pronormoblast
Basophilic Normoblast
Polychromatic Normoblast
Orthochromatic Normoblast
Polychromatic Erythrocyte
Immature Basophil
Immature Eosinophil
Immature Monocyte
Megakaryocyte
Basophil
Eosinophil
Neutrophil
Monocyte
Platelets
Erythrocyte
Lymphocyte

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

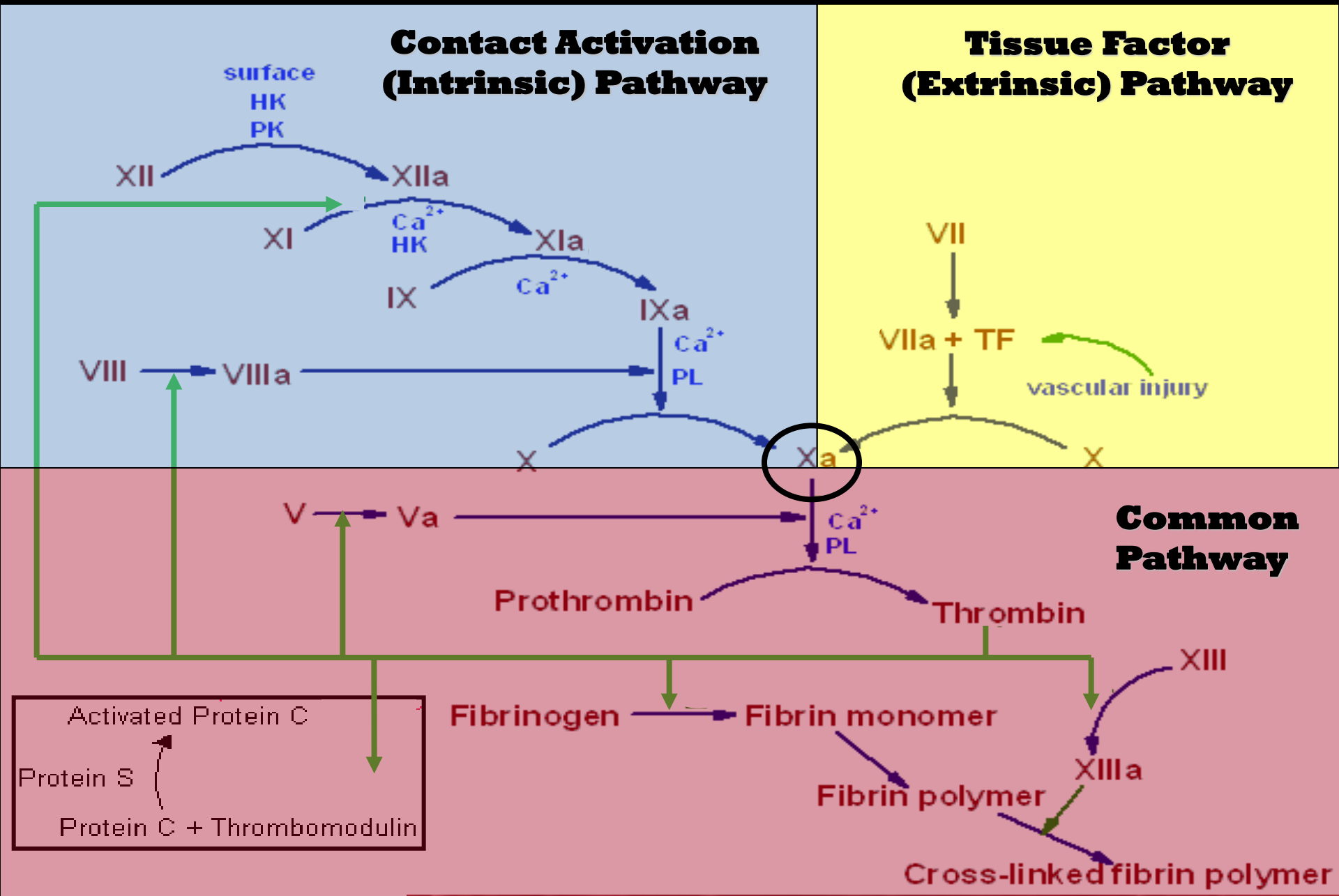
- **Nitric Oxide (NO);**
  - released from endothelial cells, macrophages, & Plt ☛ inhibit Plt activation & promotes vasodilatation

Clotting Factors

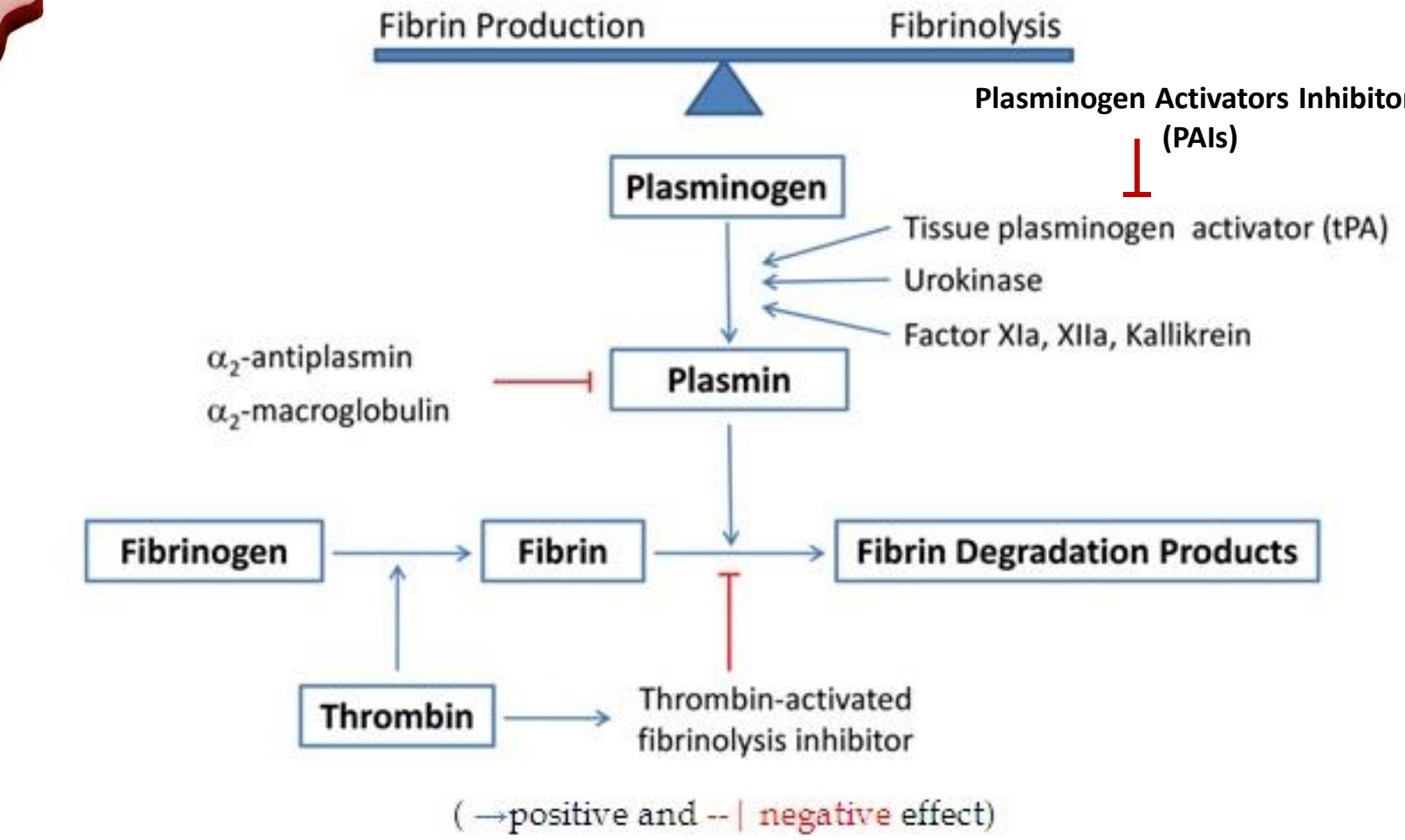
Clotting Factors in Blood and Their Synonyms

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	

Coagulation Cascade



Fibrinolysis



Hemostatic Phases

Primary Hemostasis:

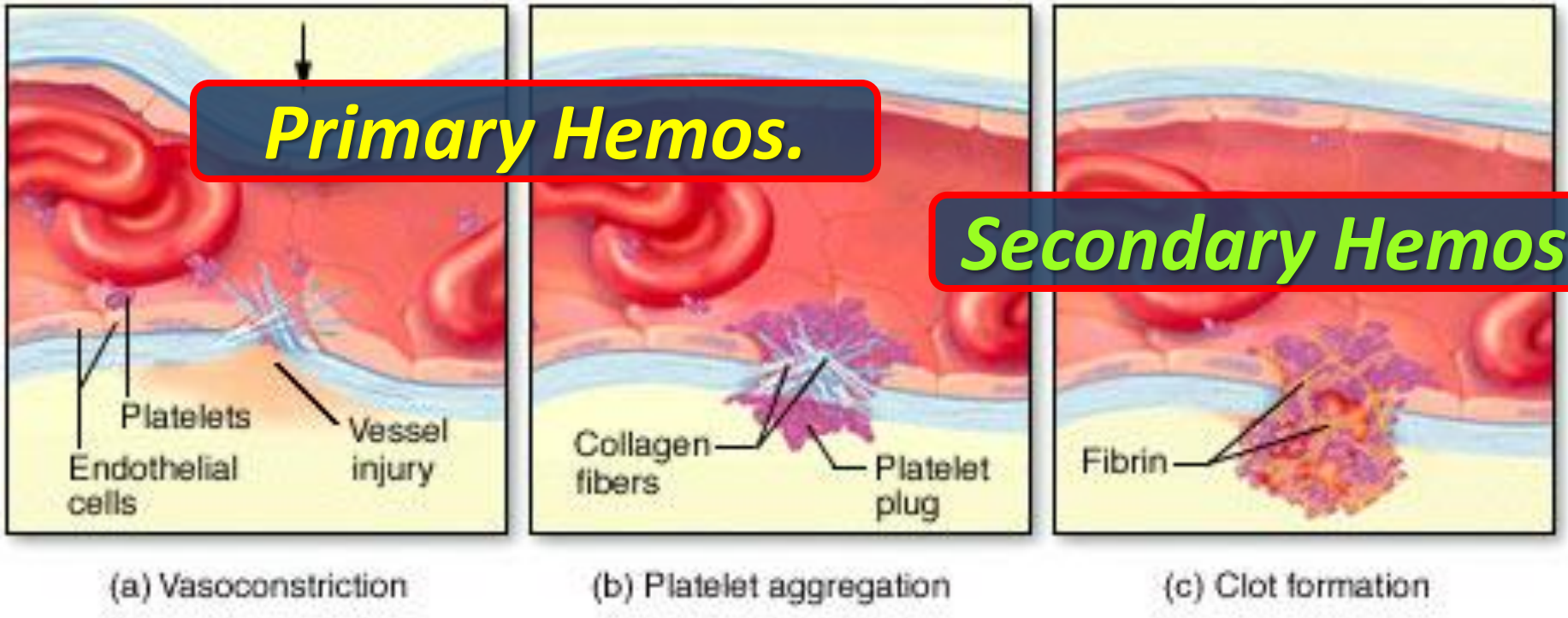
1. Endothelium Injury
2. Platelet
3. Von Willebrand Factor

Secondary Hemostasis:

1. Clotting Factors
2. Soluble Protien Fibrinogen converted to insoluble Fibrin

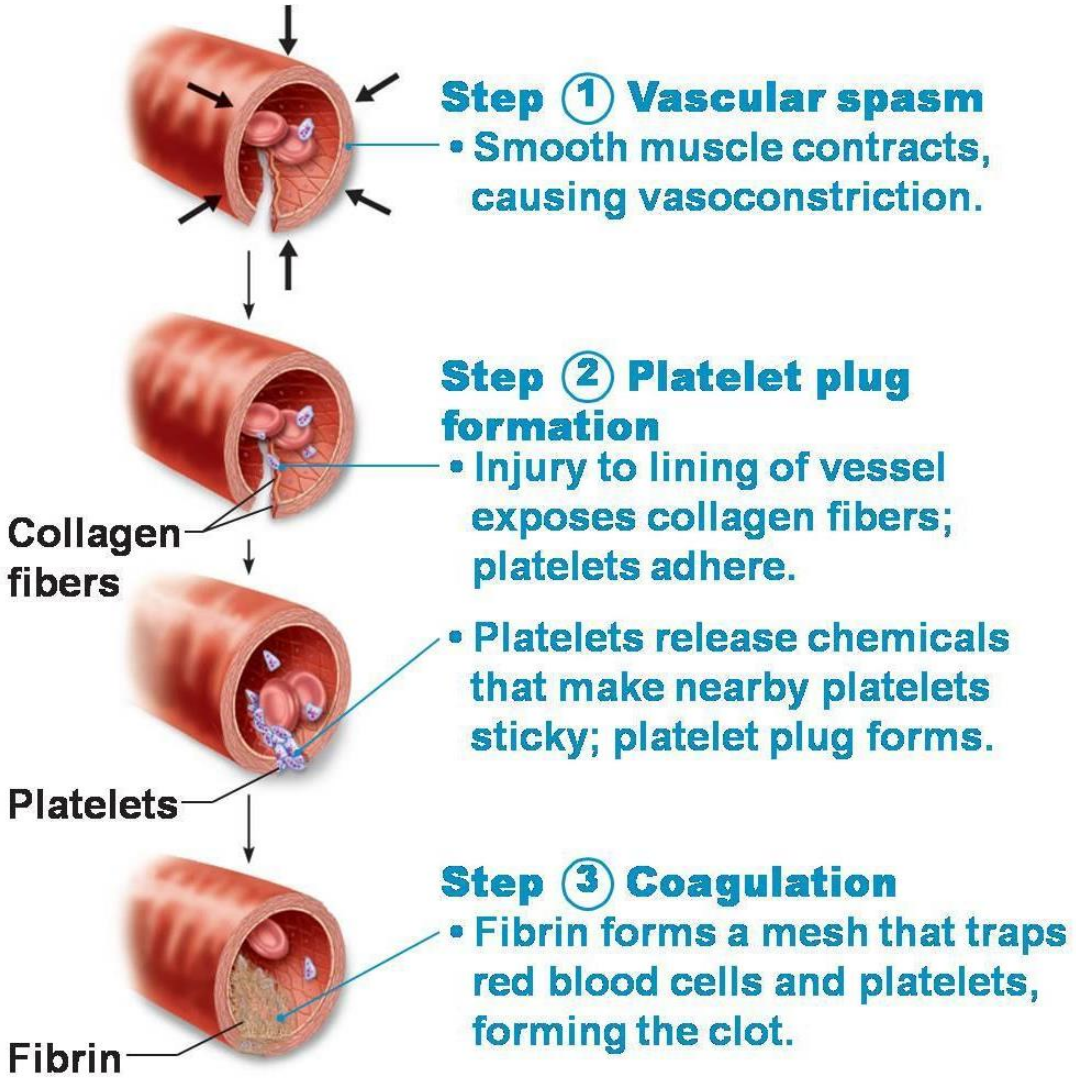
control mechanisms & removal of the clot

Hemostatic Phases



https://youtu.be/HFNWGCx_Eu4

Hemostatic Phases



CONGENITAL BLEEDING DISORDERS

Hemophilia

an inherited bleeding disorder caused by deficiency of coagulation.
(the most common inherited bleeding disorders)

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

- ***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).

Hemophilia

characterized based on the residual or baseline factor activity level (also referred to as "factor level"); expressed as a % of normal or in IU/mL.

Factor levels typically correlate with the degree of bleeding Symptoms.

- ***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**).

Hemophilia

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, ↓ Factor Level, Mixing study (corrected), N VWF & PT
Rx >> Replacement of the deficient coagulation Factor (recombinant or plasma derived) + Adjunctive therapy (Desmopressin (DDAVP), Antifibrinolytic agents (Tranexamic Acid, Aminocaproic Acid), rFVIIa (with inhibitors)

Von Willebrand Disease

The most common bleeding disorder.

Classification of von Willebrand disease

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

Von Willebrand Disease

Congenital >> 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)

PLATELETS DISORDERS

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)

PLT Disorders (Quantitative)

Causes of Thrombocytopenia

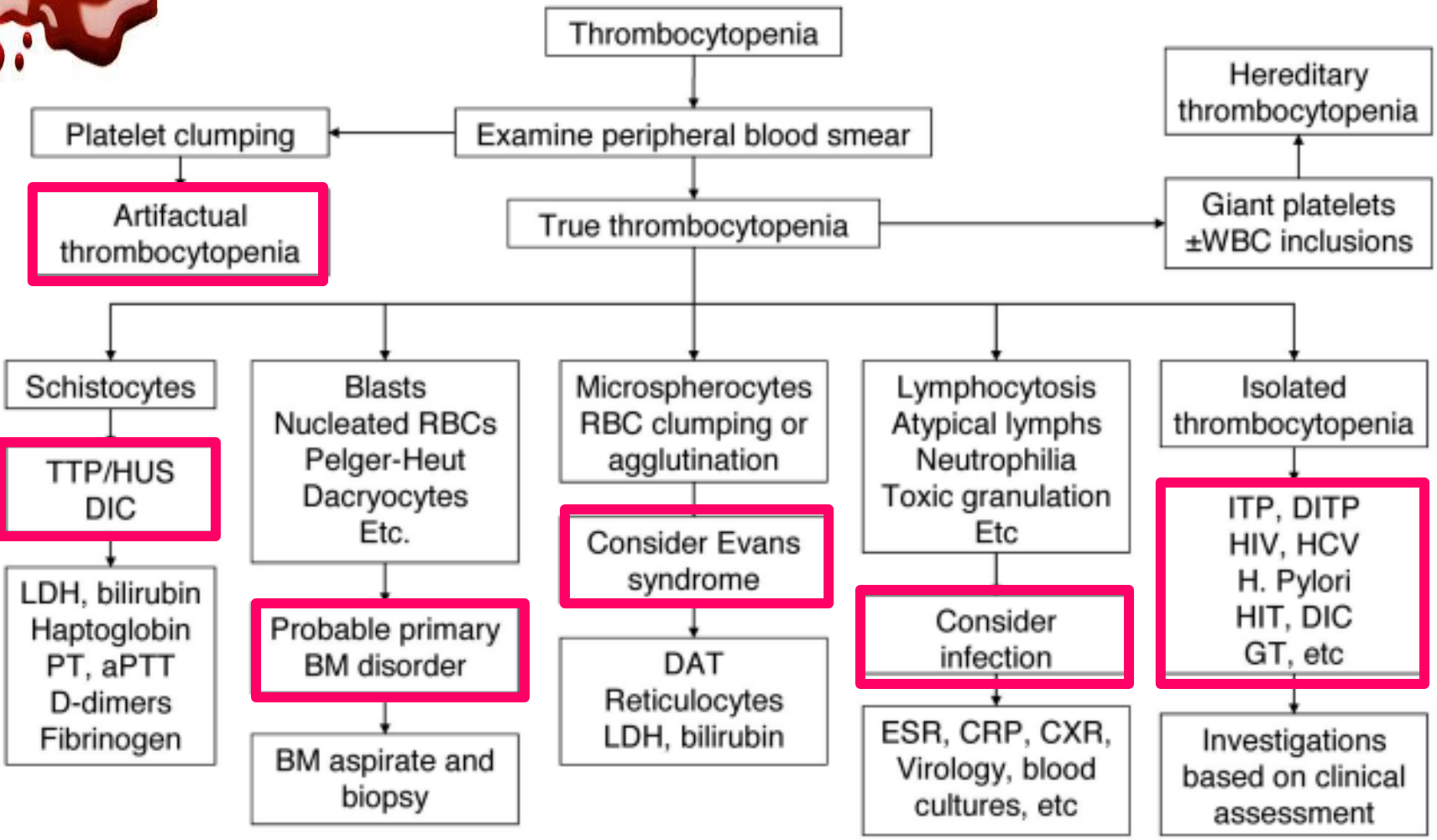
Infections
HIV
Hepatitis C
Epstein-Barr virus (EBV; can be associated with infectious mononucleosis)
H. pylori (suspected in patients with symptoms of dyspepsia or peptic ulcer disease)
Sepsis with disseminated intravascular coagulation (DIC)
Intracellular parasites (eg, malaria, babesia)
Hypersplenism 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)

Plt Disorders (Quantitative)

Causes of Thrombocytopenia

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

Approach to Thrombocytopenia



Immune Thrombocytopenic Purpura (ITP)

Primary : isolated thrombocytopenia due to immune Plt destruction & ↓ 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

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
Second-line	**Splenectomy** *(? for ITP >6 mo)*	~65% long-term remission
	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.

Pathogenesis :

massive activation of coagulation that overwhelms control mechanisms ☛ thrombosis

Acute consumption of coagulation factors & Plts ☛ bleeding

Dx >> ↑ 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

PLT DISORDERS (QUALITATIVE)

ACQUIRED PLT FUNCTIONAL DISORDERS

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

PLT DISORDERS (QUALITATIVE)

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)** (Deficiency of Dense Granules)
4. **Glanzmann thrombasthenia**
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

Approach to Pt with Potential Bleeding

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
  - Sx onset (congenital vs. acquired)
  - time required for cessation

Approach to Pt with Potential Bleeding

I. **Detailed Pt & Family Medical History** (Crucial & Vital regardless of the prior Lab testing)

- Sites of bleeding (specific or multiple)

Primary Hemostasis Defects
(PLT or vW Factor)

Secondary Hemostasis Defects
(Clotting Factors Deficiencies)

Approach to Pt with Potential Bleeding

I. **Detailed Pt & Family Medical History** (Crucial & Vital regardless of the prior Lab testing)

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

Drugs Used for Clotting Disorders

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

Drugs Used for Clotting Disorders

Antiplatelets

- 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

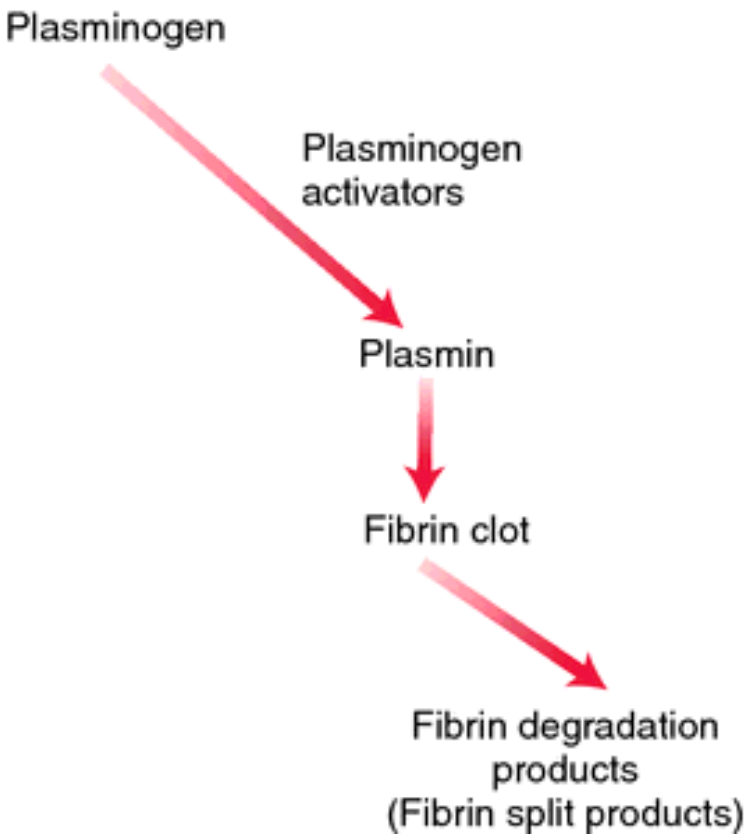
Clopidogrel	Plavix	6 hr
Cangrelor	Kengreal	3 – 6 min
Prasugrel	Effient	7 – 15 hr
Ticlopidine	Ticlid	13 hr
Ticagrelor	Brilinta	7- 9 hr

Drugs Used for Clotting Disorders

Thrombolytics

Plasminogen Activators

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



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

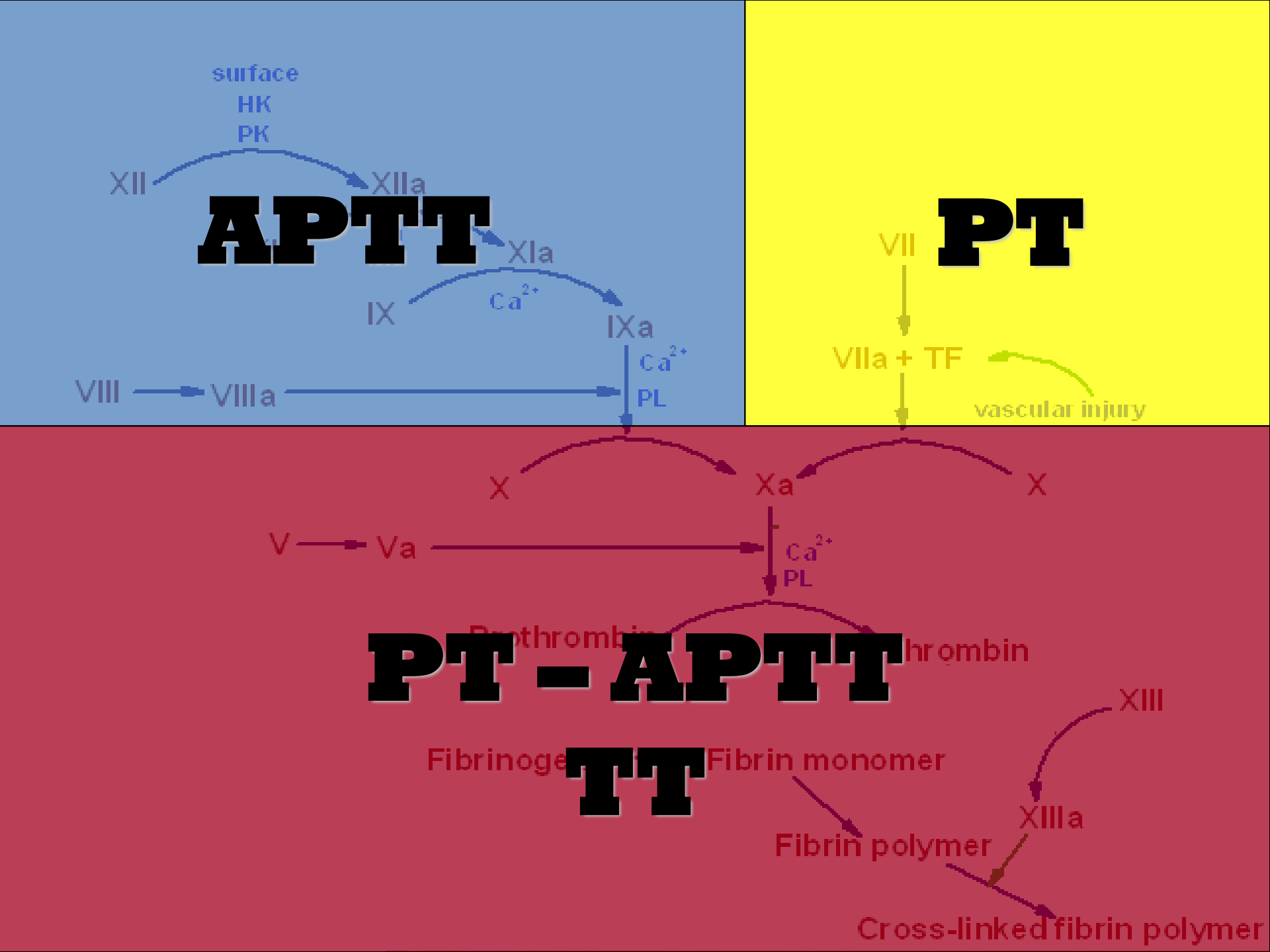
Test result		Causes of test result pattern
PT	aPTT	
Prolonged	Normal	**Inherited**
		Factor VII deficiency
		Acquired
		Mild vitamin K deficiency
		Liver disease
		Warfarin administration
		Acquired inhibitor of factor VII
		Lupus anticoagulant (more commonly causes isolated prolonged aPTT; may be associated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

Causes of Prolonged Coagulation Profile

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)

Causes of Prolonged Coagulation Profile

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


surface
HK
PK
XII
XIIa
APTT
XIa
IX
Ca2+
IXa
Ca2+
VIII
VIIIa
PL
PT
VII
VIIa + TF
vascular injury
X
Xa
X
V
Va
Ca2+
PL
hrombin
PT – APTT
XIII
Fibrinoge
Fibrin monomer
TT
XIIIa
Fibrin polymer
Cross-linked fibrin polymer

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 ")

Specialized Tests

I. **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)
II. **PLT Aggregation Tests:** (5 external aggregating factors; ADP, Collagen, Ristocetin, Arachidonic Acid, Adrenaline)
III. **Von Willebrand Factor** (Antigen & Activity)
IV. **Factor XIII assay** (F XIII Deficiency >> normal PT & PTT)
V. **Human Plasminogen Activator Inhibitor (PAI-1)**
VI. **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

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

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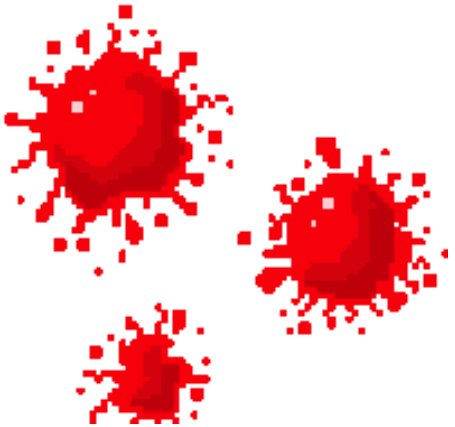
King Saud University
1957

THANK YOU

Dr. Gamal



MANAGEMENT IN THE PERIOPERATIVE STAGE

Management of Bleeding Pt

1. 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.
2. 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**.
3. 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.

Management of Bleeding Pt

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.

Management of Bleeding Pt

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.

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 ass with a 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.

Preoperative Heparin Bridging

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

PRE OP //

- **LMWH >>** discontinue 24 hours before the planned surgery or procedure, based on a biologic half-life of most subcutaneous LMWH of ~ 3-5 hours.

If a twice-daily LMWH regimen is given >> evening dose the night before surgery omitted.
if a once-daily regimen is given (Dalteparin 200 IUs/kg), ½ of the total daily dose is given on the morning of the day before surgery >> ensures that no significant residual anticoagulant will be present at the time of surgery.

- **UFH >>** Therapeutic dose IV infusion continue until 4-5 hours before the procedure, based on the biologic half-life of IV UFH of ~ 45 minutes.

If SC UFH is used (dose of ~ 250 IUs/kg BID), the last dose can be given the evening before the procedure.

Preoperative Heparin Bridging

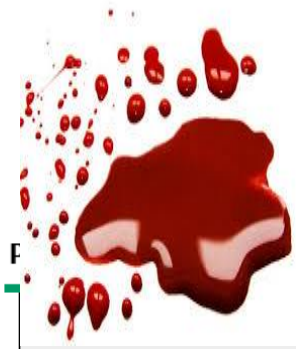
Post OP

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**.

Preoperative Management of Agents Affecting Hemostasis

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 Agents Affecting Hemostasis

ment 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				

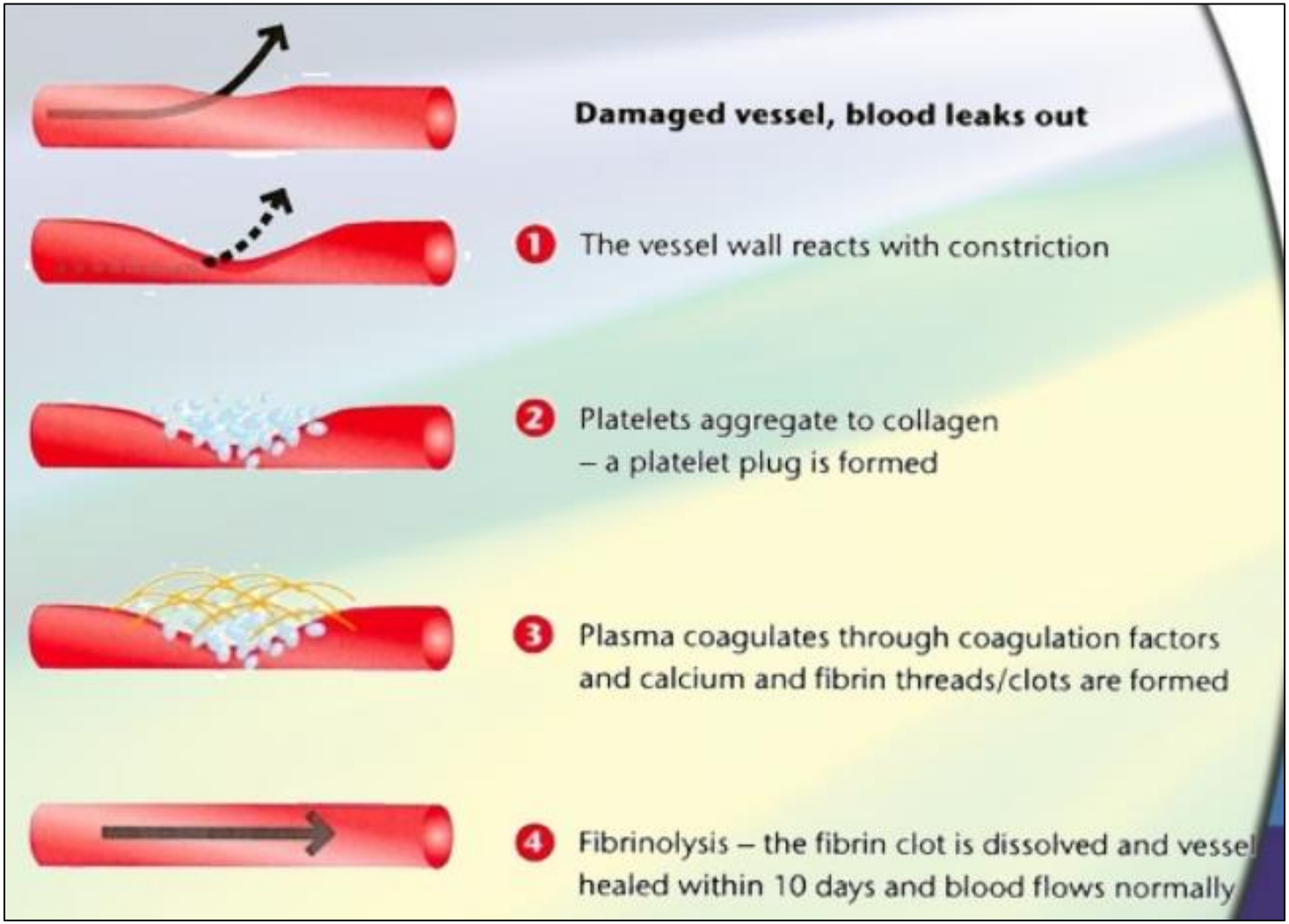
Coagulation Factor Levels Required For Hemostasis

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

INHIBITORS

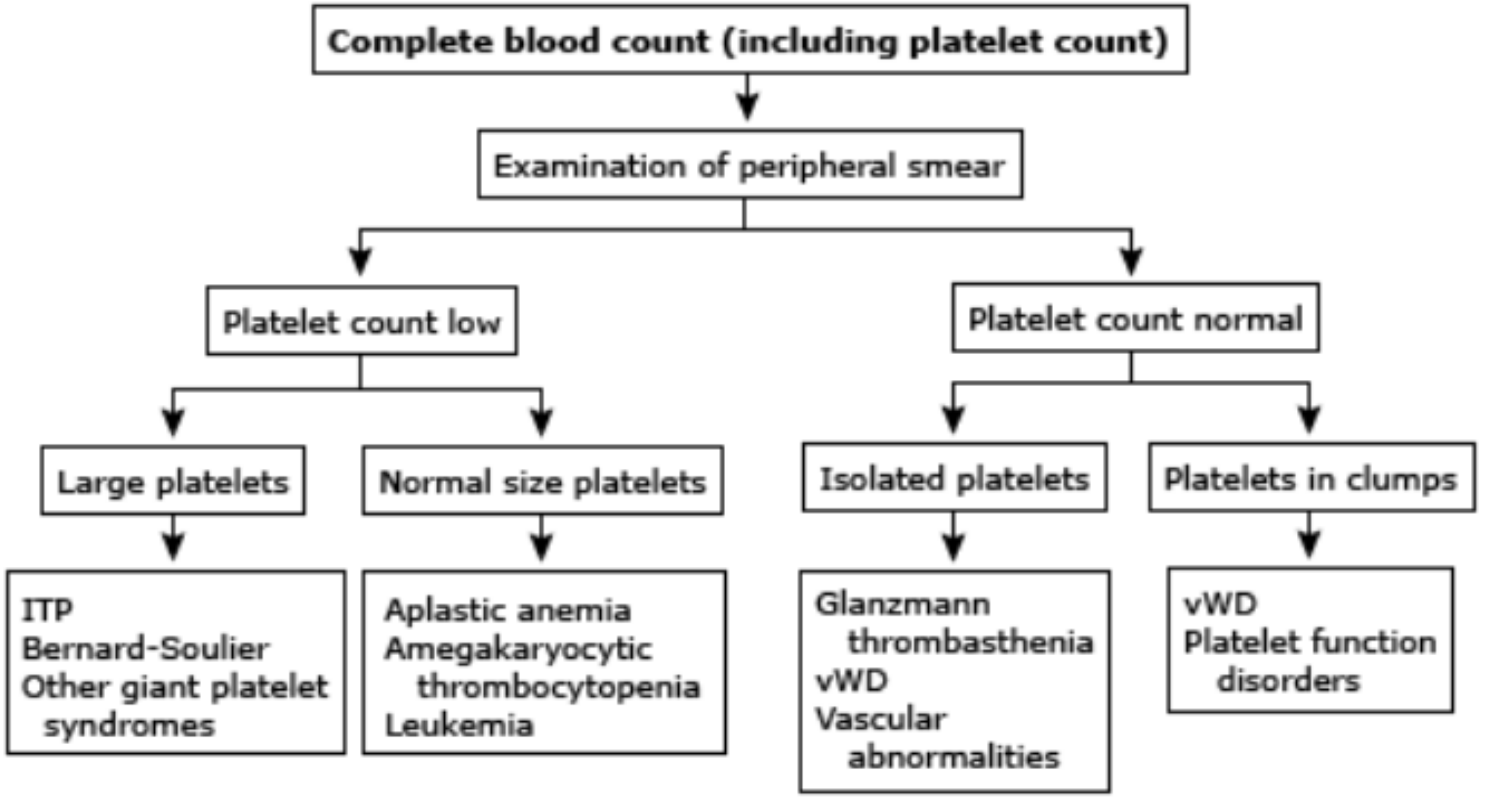
1. Antithrombin III	A serin protease inhibitor (serpin) that degrades the serine proteases; (thrombin, IXa, Xa, XIa, XIIa). Constantly active, but its adhesion to these factors is increased by the administration of heparin. Quantitative or qualitative deficiency of antithrombin (in born or acquired)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

Hemostatic Phases



Diagnostic Approach to Plt Disorders

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



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

Primary : isolated thrombocytopenia due to immune Plt destruction & ↓ 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)