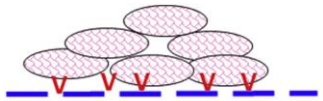
HLS pathology lecture 4

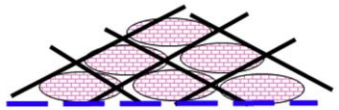
COAGULATION DISORDERS

DR. DUA ABUQUTEISH



Primary Hemostasis

Vessel/platelet/VWF interactions



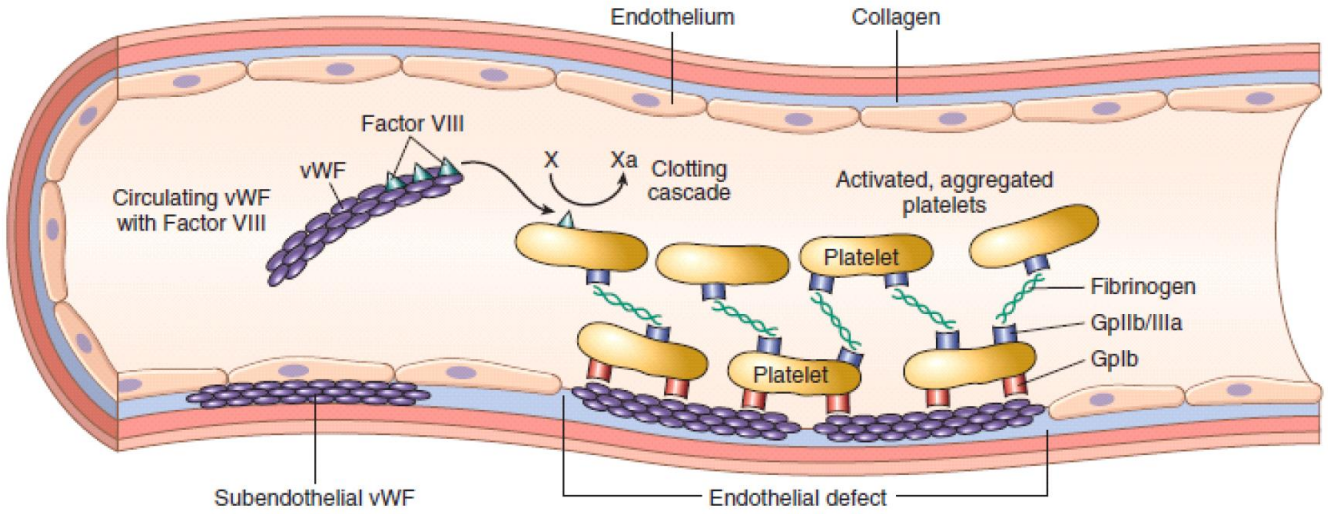
Secondary Hemostasis

Coagulation & anticoagulant factors

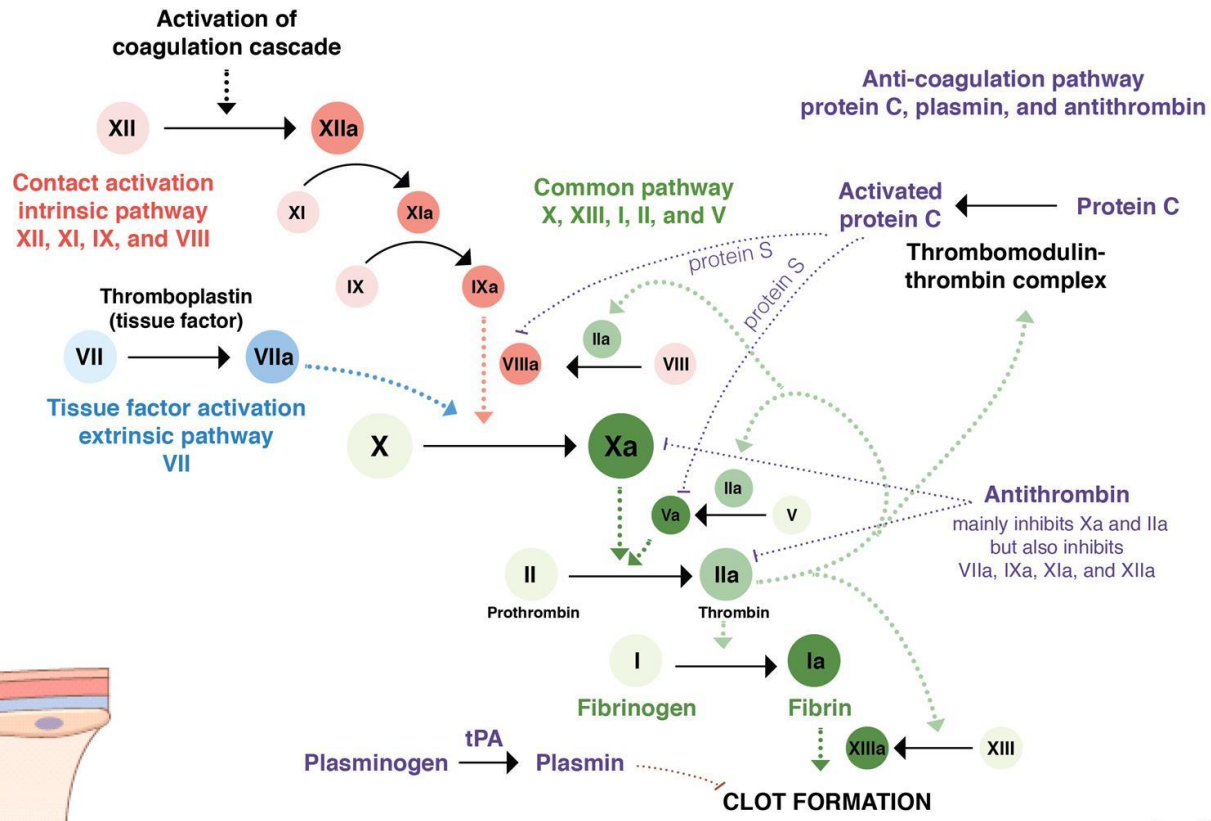
Fibrinolysis

Plasmin activation & fibrin dissolution

- Platele



Coagulation Cascade



Lucy Liu

Initial Laboratory Tests For Bleeding Abnormalities

- **Platelet count** (normal is 150,000 and 400,000 per microliter of blood)
- **Bleeding time:** to assess platelet function. It involves making a patient bleed, then timing how long it takes to stop bleeding using a stopwatch.
- **Partial thromboplastin time (PTT):** measures activity of the intrinsic clotting pathway
- **Prothrombin time (PT)/INR:** both measure activity of the extrinsic clotting pathway
- **Thrombin time (TT):** measures the final step in the clotting cascade, in which fibrinogen is converted to fibrin

Common pathway factors X, V, prothrombin (II) and fibrinogen (I): affect both PTT & PT

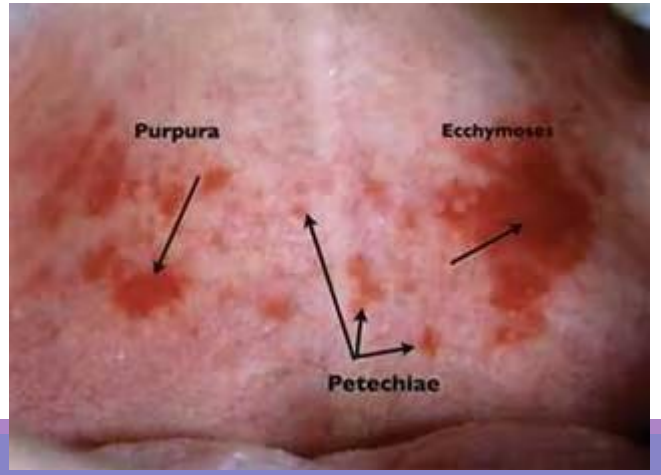
Clinical presentation; symptoms

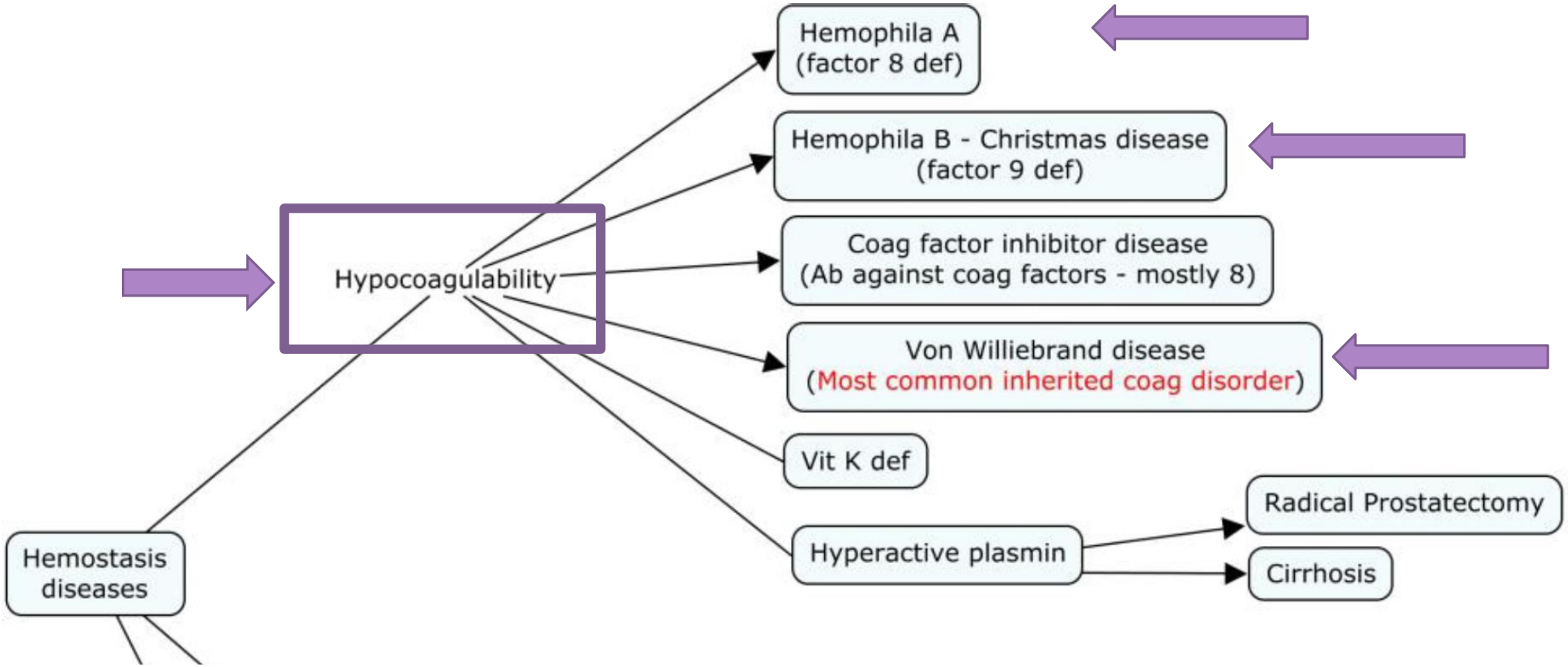
Common features of patients with problems in primary hemostasis:

- ✓Mucosal and skin bleeding; intracranial bleeding with severe thrombocytopenia
- ✓Mucosal bleeding - epistaxis (nose bleeding), hemoptysis (coughing blood), GI bleeding, hematuria, and menorrhagia (heavy menses)
- ✓Skin bleeding - petechiae (bleeding spots on skin), purpura (>3mm bleeding spots), ecchymoses, (>1cm), easy bruising.

Common features of patients with problems in secondary hemostasis:

- ✓Deep bleeding in muscles and joints
- ✓Rebleeding after surgical procedures




Hemophila A
(factor 8 def)
Hemophila B - Christmas disease
(factor 9 def)
Hypocoagulability
Coag factor inhibitor disease
(Ab against coag factors - mostly 8)
Von Willebrand disease
(Most common inherited coag disorder)
Vit K def
Radical Prostatectomy
Hyperactive plasmin
Cirrhosis
Hemostasis
diseases

Hemophilia A

- Factor VIII deficiency (hemophilia A)
- Inherited as an X-linked recessive trait
- Almost exclusively affects males
- 1 in every 10,000 births or 1 in 5000 male births
- It is characterized by mild, moderate or severe bleeding episodes (depends on factor VIII level)
- Bleeding into muscle, soft tissue or joints (hemarthrosis – 70-80%), and excessive bleeding after surgery, trauma, dental procedures or circumcision
- Petechia are characteristically absent

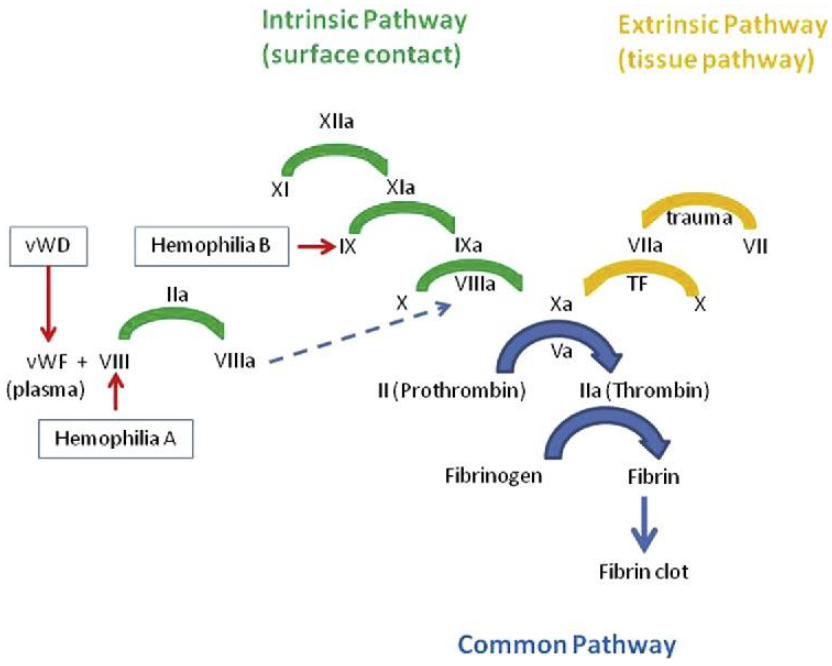
Hemophilia A

- Factor VIII in plasma circulates bound to von Willebrand factor protein. Markedly unstable in the absence of vWF.
- Factor VIII and factor IX = activate factor X, which in turn with its cofactor, factor Va, activates thrombin

Laboratory tests:

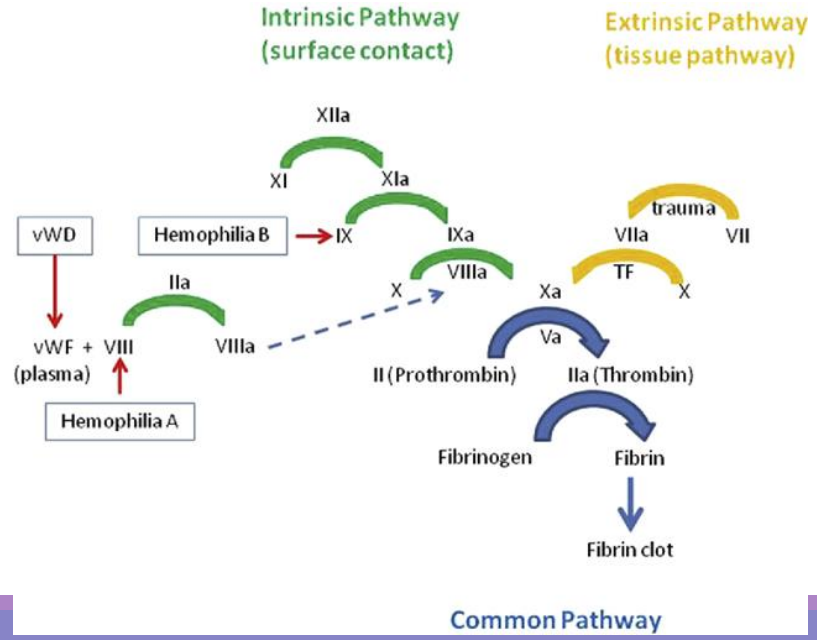
- Prolonged PTT. Normal PT and TT. Normal platelet count.

Treatment: replacement therapy (factor VIII concentrate or recombinant VIII).



Hemophilia B

- Factor IX deficiency (hemophilia B)
- Inherited as an X-linked recessive trait
- It is characterized by mild, moderate or severe bleeding episodes (depends on factor IX levels)
- Also known as Christmas disease
- Almost exclusively affects males
- 1 in 30,000 male births
- Bleeding sites: same as Hemophilia A



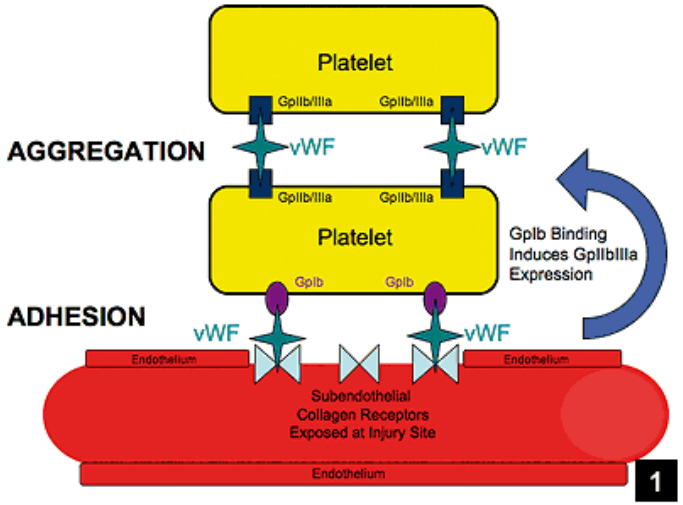
Hemophilia B

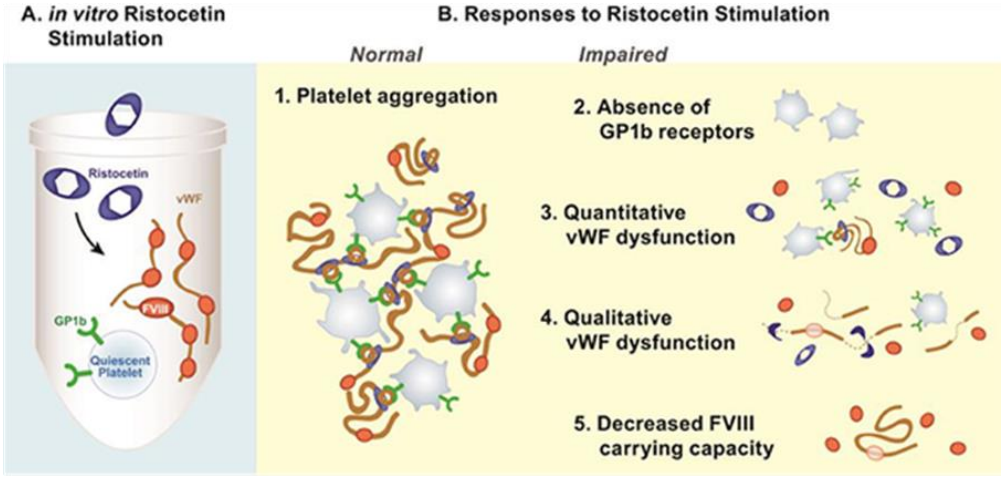
- Factor IX is a vitamin K-dependent serine protease produced in the liver
- It circulates in the plasma in its inactive form
- With factor VIIIa, it catalyzes the conversion of factor X to Xa

Laboratory tests:

- Prolonged PTT. Normal PT and TT. Normal platelet count. Normal factor VIII assay.
- ***Always measure both factor VIII and IX activity, and rule out vWD***

Treatment: Plasma-derived or recombinant factor IX concentrates





von Willebrand factor (vWF)

vWF is an adhesive protein; bridges collagen to platelets receptor GPIb and leads to formation of platelet plug

Role in coagulation (fibrin clot) vWF is required to stabilize factor VIII.

Ristocetin test: it induces platelets agglutination in the presence of vWF (RIPA)

The antibiotic ristocetin causes vWF to bind the platelet receptor glycoprotein Ib (GpIb), so when ristocetin is added to normal blood, it causes agglutination

von Willebrand disease (vWD)

- The most common hereditary bleeding disorder (prevalence 0.1-1%).
- Most cases are inherited as autosomal dominant disorder (AD).
- Mild bleeding problems - similar to a platelet function defect: mucous membrane bleeding, easy bruising, menorrhagia...

vWD : quantitative or qualitative defects of plasma vWF

Divided into 3 main type: 1,2, and 3.

- Type 1 is the most common type (70-80% of vWD cases).
- Type 3 is very rare and has most severe bleeding (don't respond to DDAVP)

von Willebrand disease (vWD)

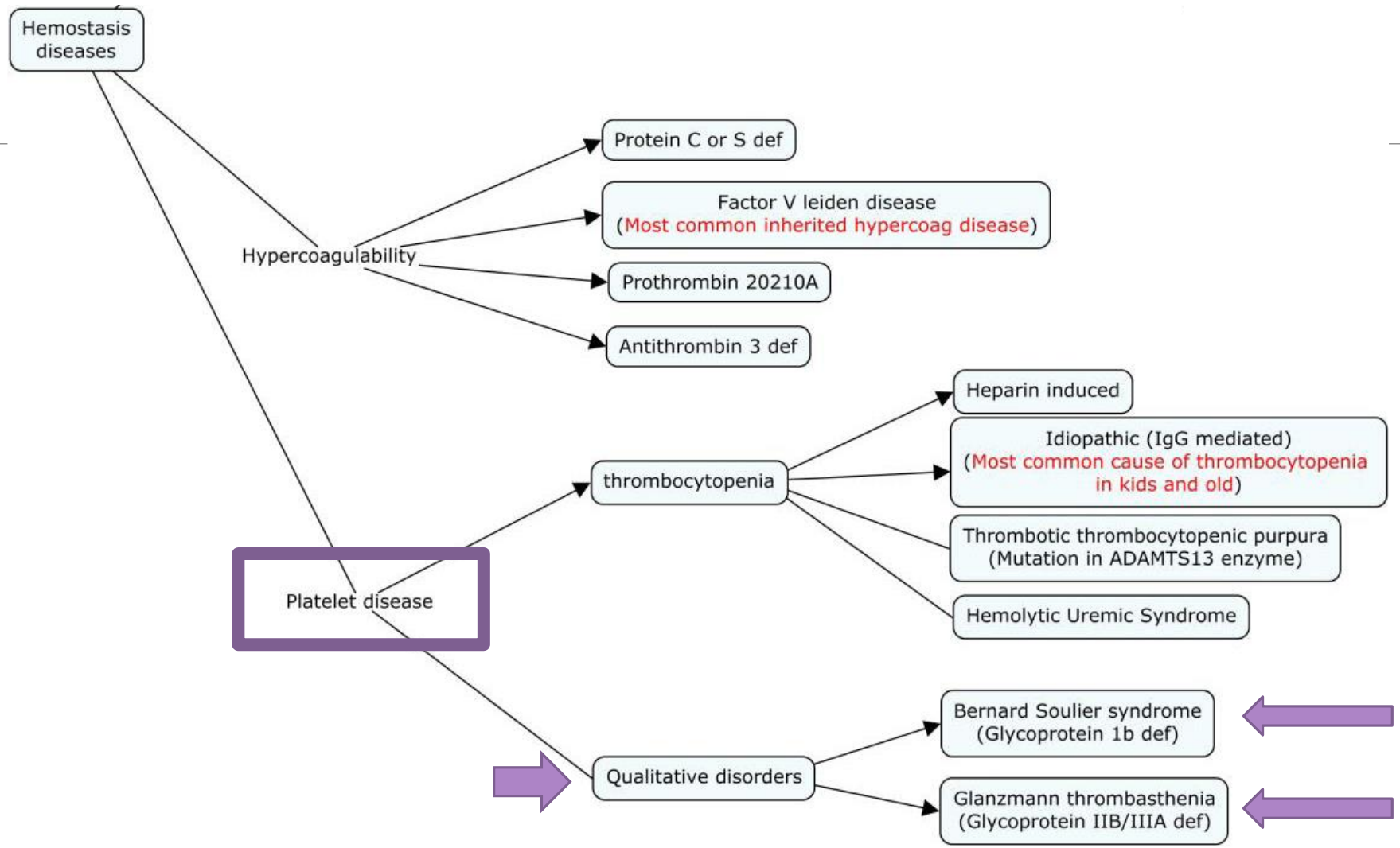
Lab results in vWD:

- ✓Increased bleeding time (BT)
- ✓Increased PTT time, normal PT (Even though their PTT is elevated, they don't get secondary hemostasis disease symptoms)
- ✓Abnormal ristocetin test

- ✓**Treatment:** Desmopressin "DDAVP" before dental work, surgery and after bleeding.
- ✓**Desmopressin "DDAVP"** temporarily increases vWF and factor VIII levels 2 - 3x

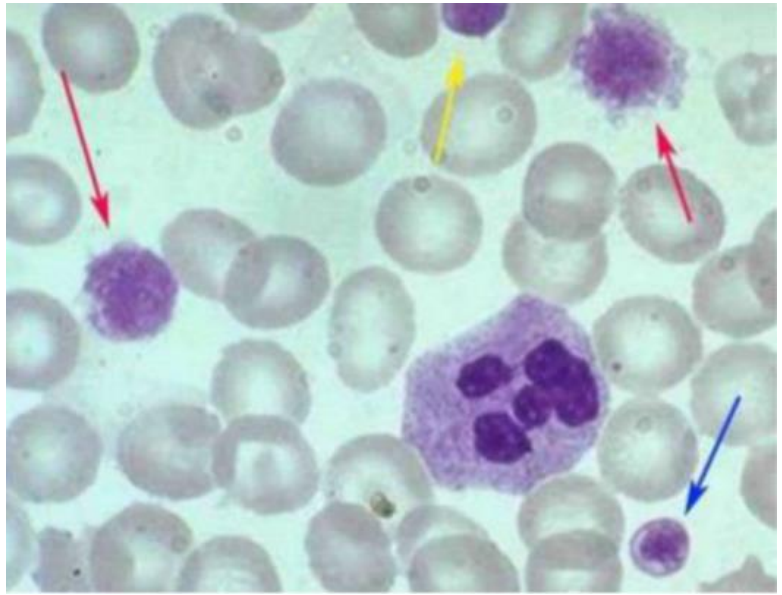
vWD differs from classic Hemophilia A in 3 cardinal manifestations:

1. AD rather than x-linked
2. Prolonged bleeding time (BT)
3. Mucocutaneous bleeding rather than hemarthroses and deep muscle hemorrhage.


Hemostasis diseases
Hypercoagulability
Protein C or S def
Factor V leiden disease
(Most common inherited hypercoag disease)
Prothrombin 20210A
Antithrombin 3 def
Platelet disease
thrombocytopenia
Heparin induced
Idiopathic (IgG mediated)
(Most common cause of thrombocytopenia in kids and old)
Thrombotic thrombocytopenic purpura
(Mutation in ADAMTS13 enzyme)
Hemolytic Uremic Syndrome
Qualitative disorders
Bernard Soulier syndrome
(Glycoprotein 1b def)
Glanzmann thrombasthenia
(Glycoprotein IIB/IIIA def)

1.Bernard Soulier syndrome

- Genetic GP1b deficiency; platelet adhesion is impaired
- Autosomal recessive disease



Lab and blood smear show:

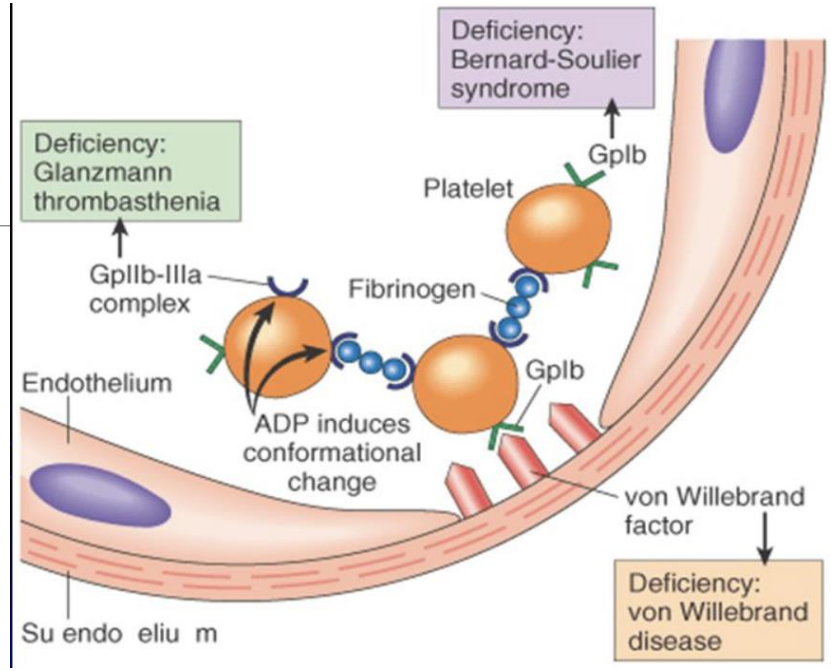
- Mild thrombocytopenia (platelets have a short life because they lack GP1b)
- Enlarged (giant) platelets
- Prolonged BT

Tests:

✓Platelet aggregation in response to ADP is normal

✓Absent platelet aggregation in response to vWF and ristocetin

2. Glanzmann's thrombasthenia



- ➢Genetic GIIB/IIIA deficiency; platelet aggregation is impaired
- ➢ Autosomal recessive disease

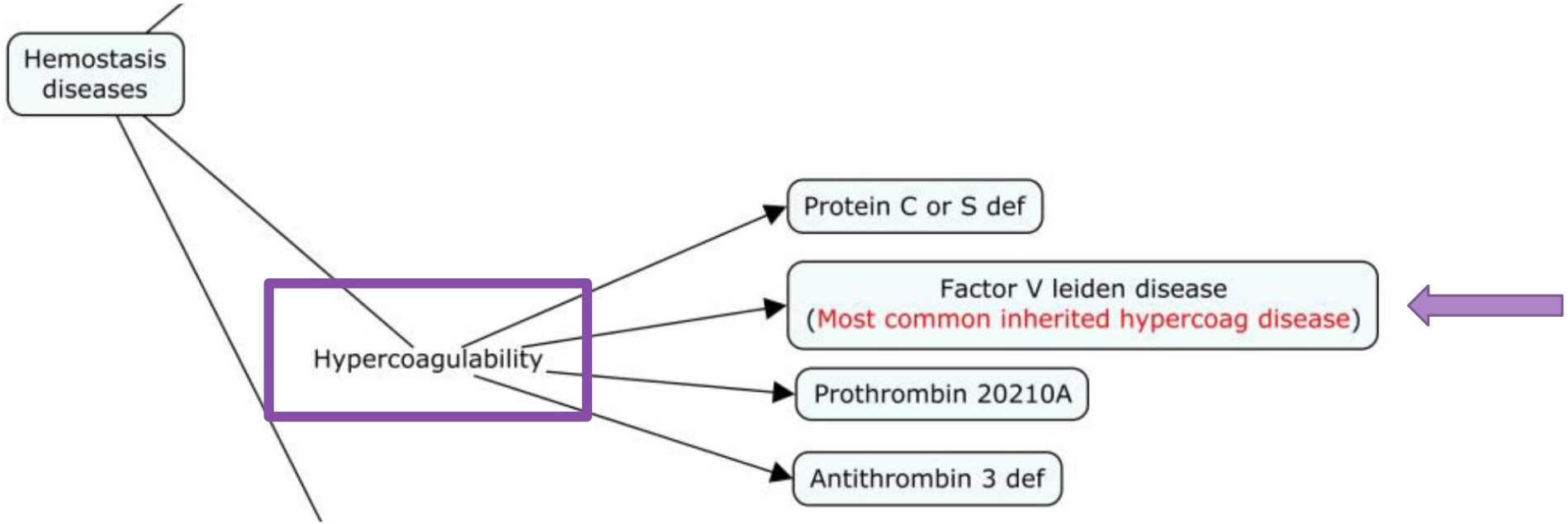
Labs and blood smear shows:

- Normal platelet count and morphology
- Prolonged BT

Tests:

- ✓Failure to aggregate in response to ADP
- ✓There is normal platelet aggregation in response to vWF and ristocetin

	Ristocetin drug + pt blood
vWF disease	- No agglutination
Bernard-Soulier (Gly Ib deficiency)	- No agglutination
Glanzmann thrombasthenia (Gly IIb/IIIa deficiency)	- Yes agglutination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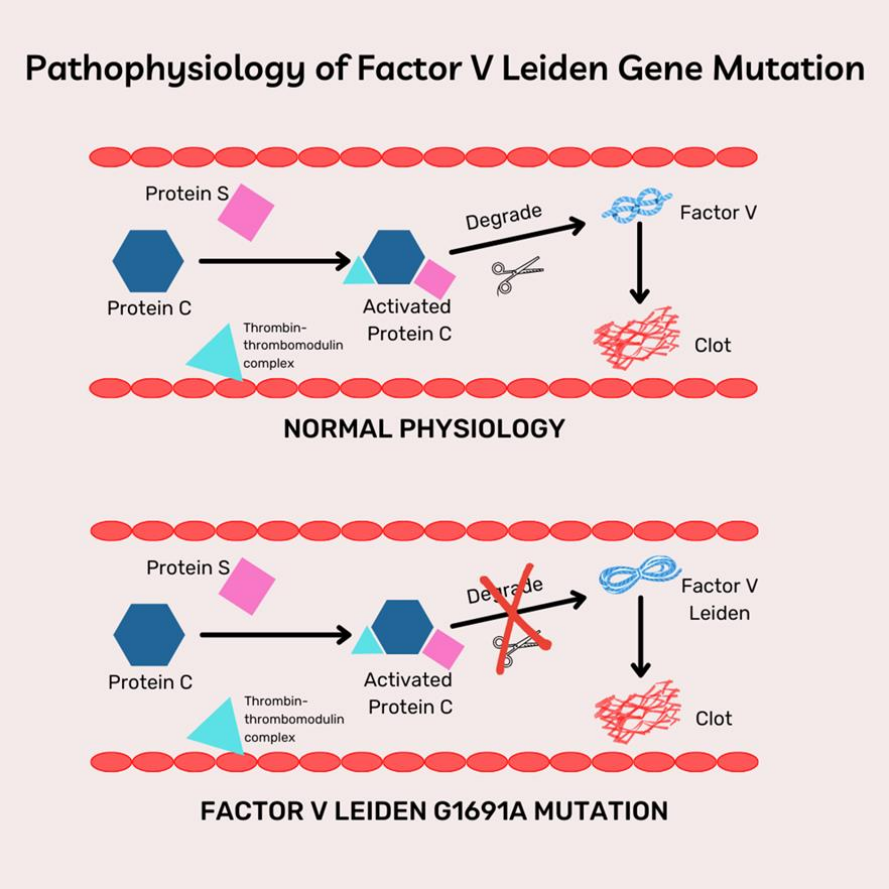
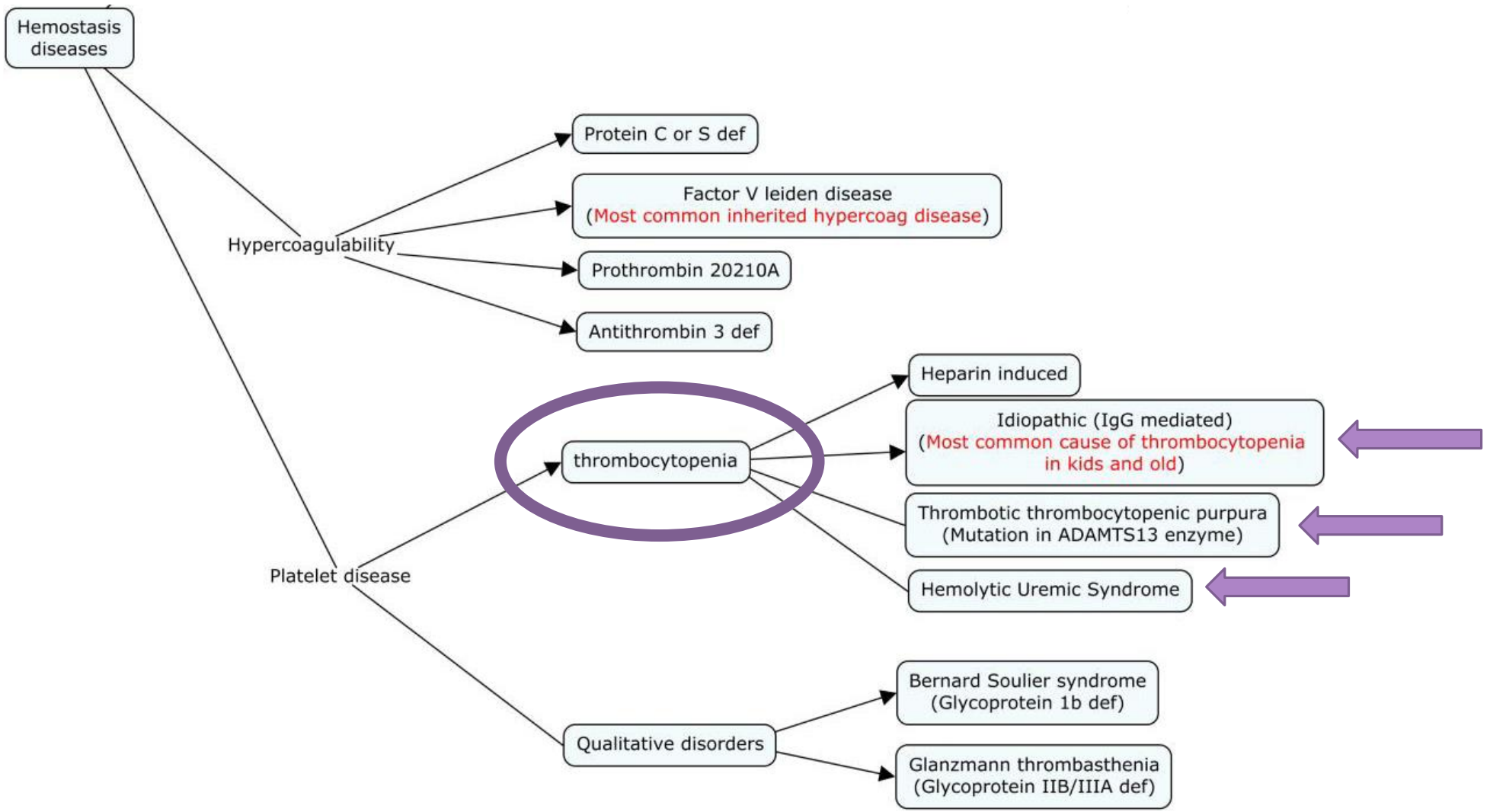
Factor V leiden disease
(Most common inherited hypercoag disease)
Prothrombin 20210A
Antithrombin 3 def

Factor V Leiden disease

- Most common inherited cause of hypercoagulability
- There is mutations in the factor V gene
- Approximately 2% to 15% of whites carry a **specific factor V mutation (called the Leiden mutation)**. The mutation alters an amino acid residue in factor V and renders it resistant to protein C.
- Other causes of hypercoagulability include deficiencies of anticoagulants such as protein C or protein S (rare) and antithrombin III

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Thrombocytopenia

Normal range 150-450X10^3 per µl.

Levels above 60x10^3/µl will not cause bleeding under normal conditions.

Levels below 20x10^3/µl will cause: Petechiae, mucosal bleeding, Post-operative bleeding, CNS bleeding.

Levels around 5x10^3/µl can lead to fatal CNS or GI hemorrhage.

Levels between 20 and 60x10^3/µl may cause bleeding (depending on platelets functional status).

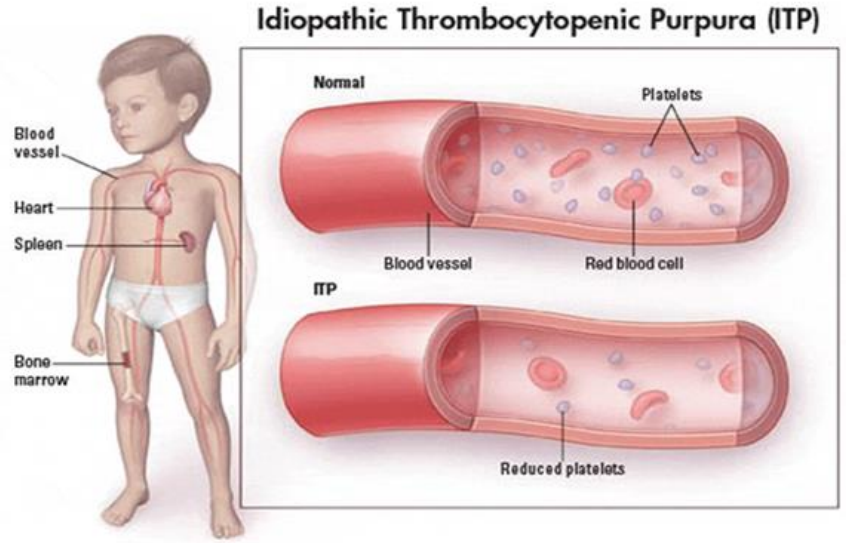
Causes of thrombocytopenia:

- Failure of production (aplastic anemia, radiation, chemo.Rx)
- Increased platelet destruction (ITP)

Thrombocytopenia is characterized by prolonged bleeding time, and a normal PT and PTT

Acute ITP (Idiopathic/Childhood)

- ✓Affects children.
- ✓Develops acutely with 1-2 week duration.
- ✓Bruising and petechia
- ✓Preceded by infection or vaccination in 75% of cases.
- ✓Formation of anti-platelets antibodies, IgG against (ex- GP IIB/IIIA)
- ✓Initial platelet count <20,000
- ✓Self limited - spontaneous remission in >90% of cases.
- ✓Severe cases benefit from steroids or IV immunoglobulins.



Chronic Immune Thrombocytopenic Purpura (ITP)

- High incidence in women of childbearing age (20-50).
- NO recent history of drug or recent infection.
- Mostly idiopathic, secondary causes include SLE, HIV, CLL, Hodgkin's disease, drugs (uncommon).
- Autoantibodies against GP IIb/IIIa, or Ib/IX (30% of cases).
- Petechial bleeding, easy bruising, menorrhagia

ITP - Diagnosis and treatment

Decreased platelet count (10-50x10^9/l), with normal Hb. and WBCs counts

Peripheral blood smear **shows large platelets**

Bone marrow shows: **Increased Megakaryocytes numbers.**

Prolongation in BT (bleeding time)

Serum : antiplatelet antibodies

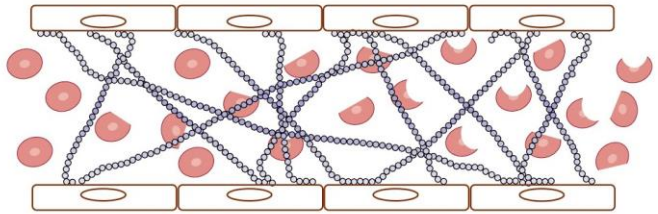
Treatment

- Splenectomy (long term treatment)
- High dose IV immunoglobulins
- Steroids and immunosuppressive therapy

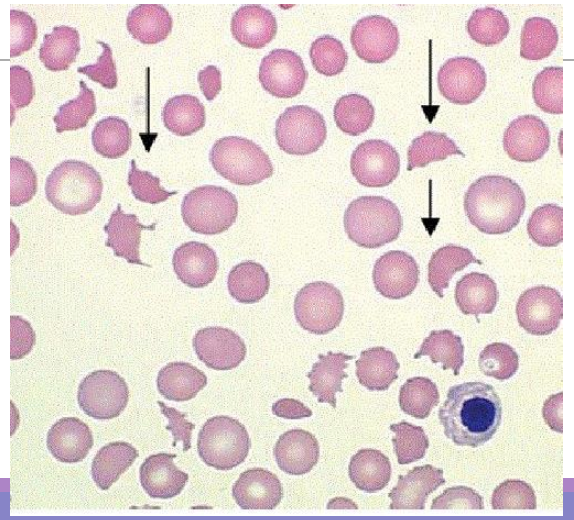
Microangiopathic Thrombocytopenia

- ✓ **Hemolysis in small blood vessels**
- ✓ Platelet microthrombus are formed in small blood vessels that cut RBCs as it passes through (**Mechanical effect**).
- ✓ This results in hemolytic anemia with **Schistocytes**, aka **helmet cells.**

Microangiopathic Hemolytic Anemia



- ✓ Thrombocytopenia is seen because of the formation of tons of microthrombi, resulting in platelet consumption



MICROANGIOPATHIC HEMOLYTIC ANEMIA (MAHA)

TTP (Thrombotic thrombocytopenic purpura)

HUS (Hemolytic Uremic Syndrome)

DIC (disseminated Intravascular Coagulation)

TTP and HUS: platelet activation (coagulation pathway not activated)

DIC: activation of coagulation pathway (prolonged PT, PTT)

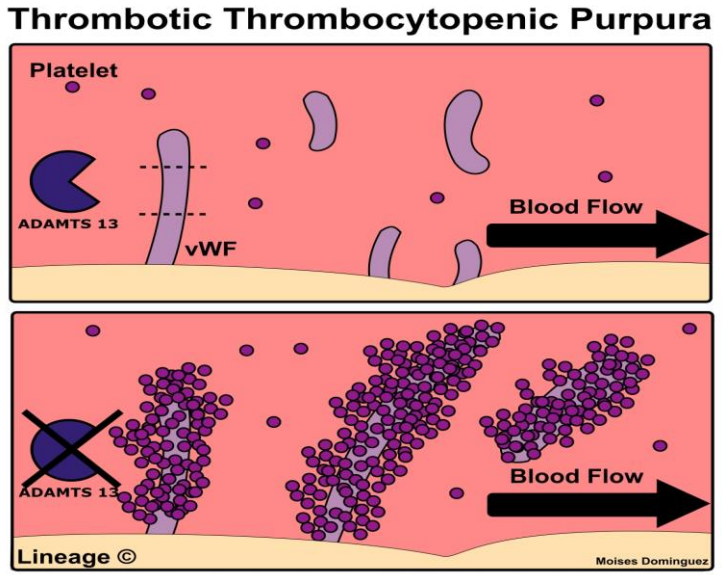
Thrombotic thrombocytopenic Purpura (TTP)

Thrombocytopenia and **Microangiopathic hemolytic anemia** characterize this disorder

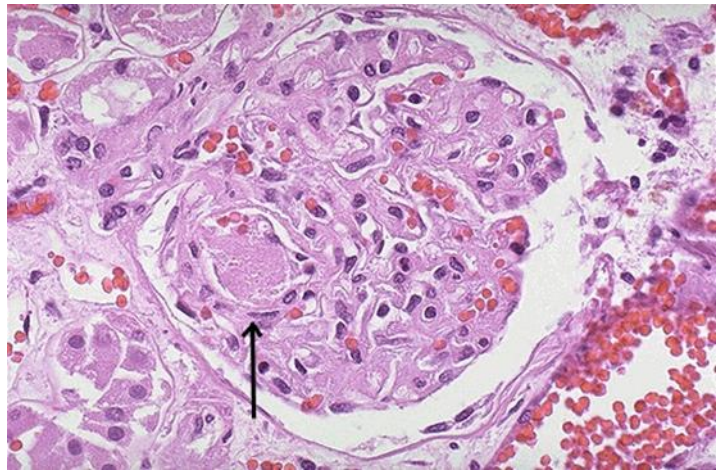
- Usually affects adults- can be Inherited and Sporadic (more common)
- **Autoantibody against ADAMTS 13**
- ADAMTS13 normally cleaves vWF multimers for eventual degradation. Deficiency of ADAMTS13 leads to increase in vWF, thus, more platelet adhesion resulting in microthrombi.
- Platelet micro-aggregate (Hyaline microthrombi) formation.

Remember these 5 symptoms: acute Thrombocytopenia, fever, microangiopathic hemolytic anemia, neurologic abnormalities, renal dysfunction.

Thrombotic thrombocytopenic Purpura (TTP)



- Diagnosis should be suspected in any patient who presents acutely with thrombocytopenia.
- Female > males, 3rd-4th decade
- **Hyaline (platelet rich) microthrombi** are the characteristic pathologic feature



Thrombotic thrombocytopenic Purpura (TTP)

Laboratory Results:
Microangiopathic hemolytic anemia picture;
Schistocytes
Reticulocytosis
Normocytic normochromic anemia
Increase Megakaryocytes in bone marrow

Signs of hemolysis:
Increase LDH
Increase indirect bilirubin
Decrease Haptoglobin

Normal PT, PTT, D-Dimer but elevated BT (bleeding time).

Treatment: Plasma exchange

Hemolytic Uremic Syndrome (HUS)

NON-IMMUNE THROMBOCYTOPENIA

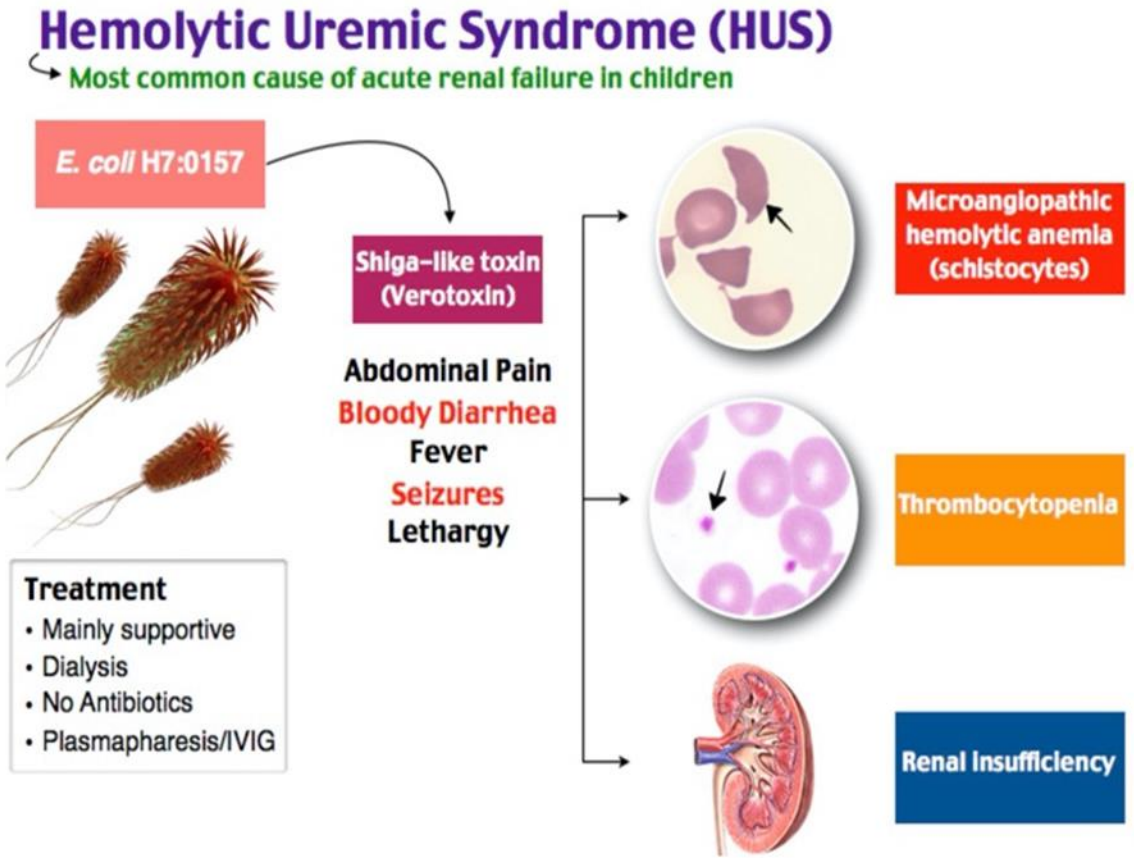
- More commonly seen in pediatric population.
- E. coli O157:H7 (toxin induced endothelial damage)
- **Bloody diarrhea** followed by **acute renal failure (UREMIA).**
- Platelet microaggregate (Hyaline microthrombi) formation, usually limited to the glomerular capillaries.
- **Acute Thrombocytopenia, Microangiopathic hemolytic anemia, Renal failure**.
- Normal PT, PTT, D-Dimer but elevated BT.
- Treatment: conservative (dialysis, antihypertensive,…).

Hemolytic Uremic Syndrome (HUS)

Hemolytic Uremic Syndrome (HUS)

Resemble TTP but:

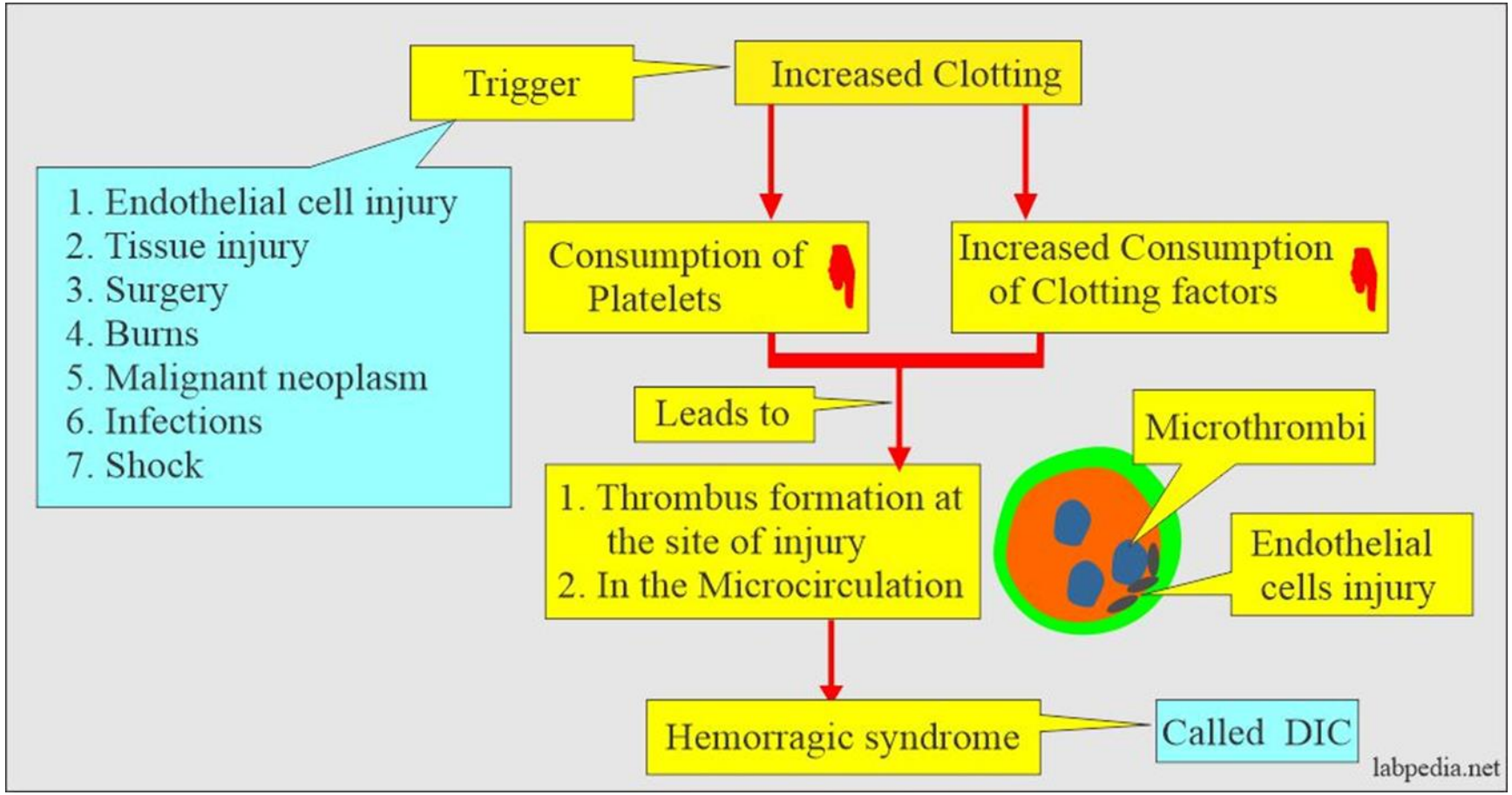
- More seen in pediatric population
- After viral/bacterial infection
- Neurological symptoms are more common in TTP
- Usually, HUS is limited to Kidney

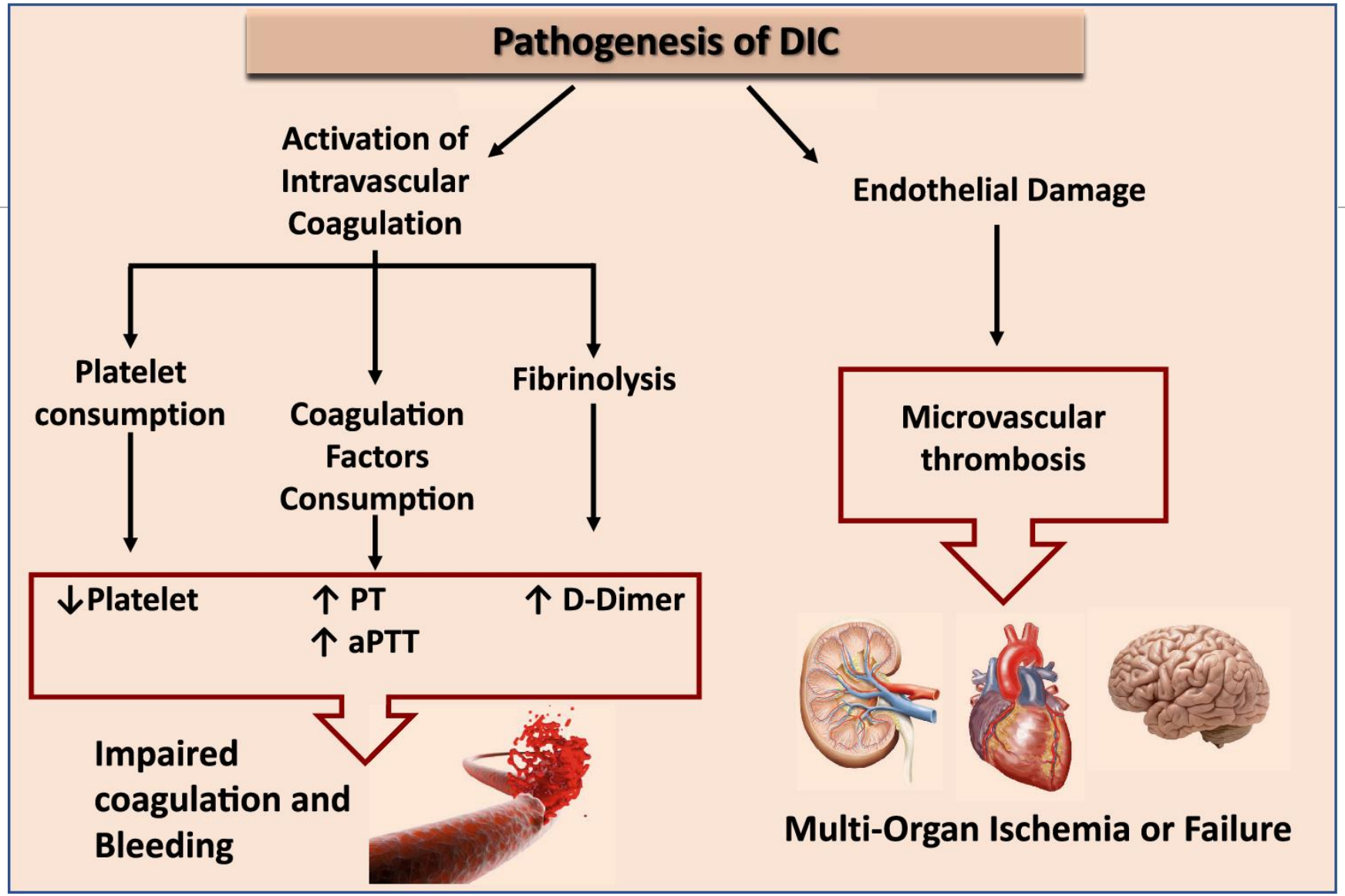


Disseminated intravascular coagulation (DIC)

- ✓DIC is a **thrombo-hemorrhagic disorder**, characterized by systemic activation of the coagulation cascade by various stimuli , **with hundreds of thrombi occluding microcirculation leading to hypoxia and microinfarcts**
- ✓Also called **consumptive coagulopathy**, **followed by bleeding due to consumption of platelets & clotting factors in blood**
- ✓Mechanism of DIC is wide-spread endothelial cell damage
- ✓ DIC is not a primary disease but rather is a potential complication of any condition associated with widespread endothelial cell damage
- ✓The major causes of which including obstetric complications, infections , neoplasms , massive tissue injury & others .

Disseminated intravascular coagulation (DIC)




Pathogenesis of DIC
Activation of Intravascular Coagulation
Endothelial Damage
Platelet consumption
Coagulation Factors Consumption
Fibrinolysis
Microvascular thrombosis
↓Platelet
↑ PT
↑ aPTT
↑ D-Dimer
Impaired coagulation and Bleeding
Multi-Organ Ischemia or Failure

Disseminated intravascular coagulation (DIC)

- Without adequate treatment, DIC can eventually lead to multiorgan dysfunction failure
- Patients can present with bleeding, thrombosis or both
- Septic patients are more likely to have thrombosis than bleeding

Lab:

- **Prolonged prothrombin time (PT), activated partial thromboplastin time (APTT) and thrombin time (TT)**
- **Elevated D dimers and other fibrin degradation products**