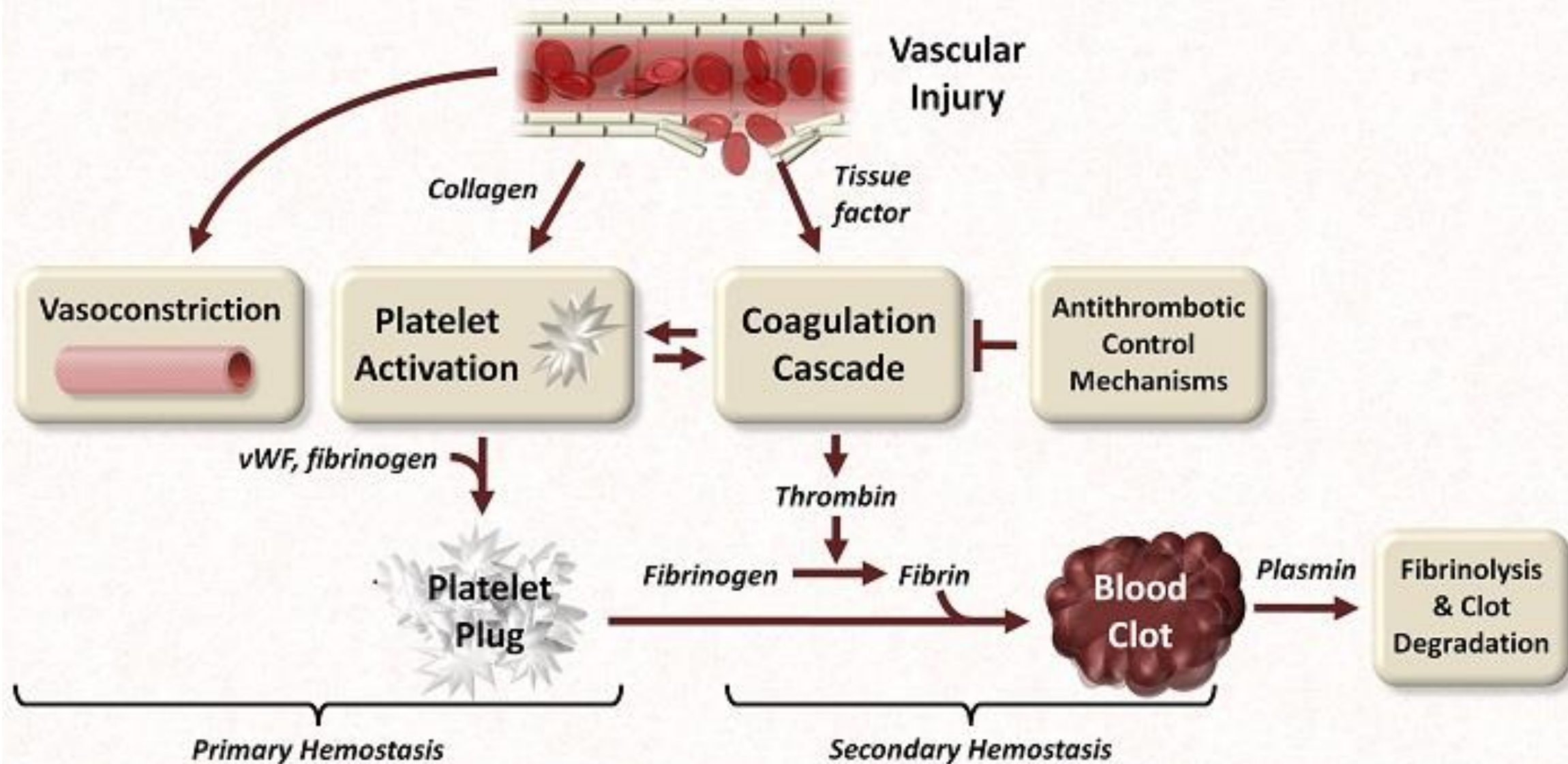


# Approach to the child with bleeding

**Abdulahadi Alzaben, MD**

**Pediatric hematology oncology and stem cell  
transplant**

# Major Components of Hemostasis



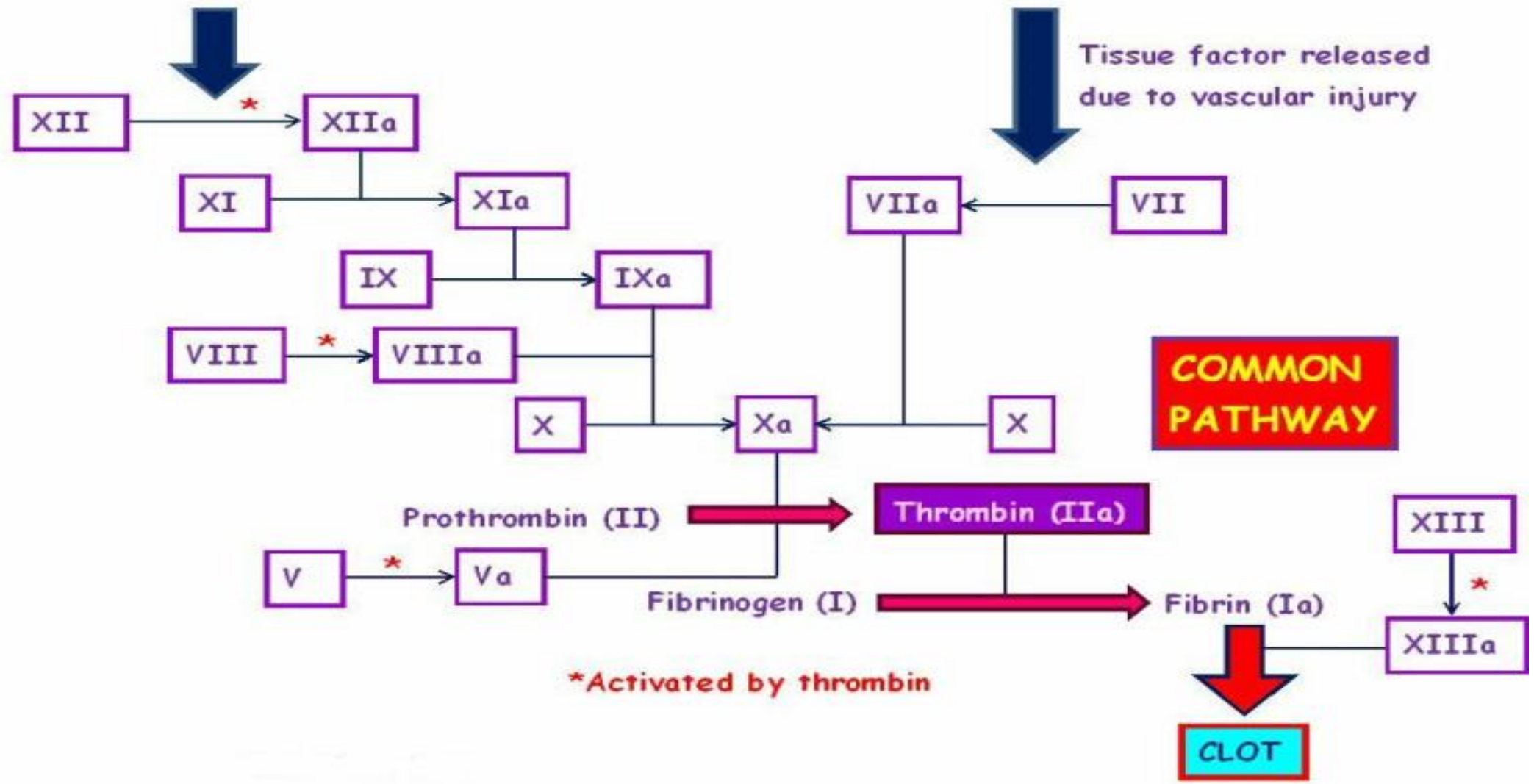
Activated by internal damaged surface

### INTRINSIC PATHWAY

Activated by TISSUE FACTOR

### EXTRINSIC PATHWAY

Tissue factor released due to vascular injury



\*Activated by thrombin

# Functional Classification of Bleeding Disorders

- **Abnormal vessels**

  - Ehler Danlos

  - HSP

- **Defects of platelets**

  - Number: Infection, ITP, Leukemia

  - Function: vWD, BS, GT, Drugs

- **Abnormal coagulation**

  - Congenital: Hemophilia A or B

  - Acquired: Liver disease, Vit K def, DIC















<b>Clinical findings</b>	<b>Disorders of coagulation*</b>	<b>Purpuric disorders •</b>
Skin - petechiae	Not usually seen	Characteristic
Ecchymosis	Common - large one or more	Characteristic - small or many scattered
Soft tissue hematoma	Characteristic	Rare
Joint hemorrhages	Characteristic - hallmark of the disease	Not usually seen
Delayed bleeding	Common	Rare
Bleeding from superficial skin abrasions	Uncommon	Common and persistent
Family history of bleeding	Common	Rare
Sex of the patient	Predominantly male	Predominantly female

# History

Neonatal bleeding

Bleeding after circumcision

Delayed bleeding from umbilical stump (factor XIII)

Epistaxis Unilateral vs bilateral

Tooth extraction, tonsils

Site of bleeding: skin, mm, joints

Family history of bleeding disorders

Drug exposure

Injury child abuse

- A male infant who is starting to walk and presents with a painful swollen joint after a fall has hemophilia until proven otherwise.
- An adolescent girl who presents with excessive menstrual bleeding, recurrent nosebleeds, and pallor may have von Willebrand Disease (vWD), the most common inherited bleeding disorder
- A five-year-old child who is not clinically ill but presents with moderate mucocutaneous purpura in the wake of a viral infection most likely has acute post-infectious immune thrombocytopenia

- A teenage girl with easy bruising and mild pallor presenting to a pediatrician's office with a strong family history of autoimmune disorders may have chronic ITP
- A ten-day-old infant with bleeding from the umbilical stump should be evaluated for factor XIII deficiency ,Intracranial hemorrhage in an infant without other risk factors should also prompt consideration of this diagnosis.

# Physical examination

Petichiae

Ecchymosis

Joint bleeding and deep seated hematomas

Significant lymphadenopathy

Hepatosplenomegaly

Active and playful vs ill looking

Telangiectic vessels

Hemangiomas

Loose joints associated with easy bruising (Ehlers-Danlos syndrome)

# Diagnosis of Coagulation Disorders Screening Tests

- **Complete blood count**
- Thrombocytopenia when less than 150,000/mm<sup>3</sup>
- Thrombocytopenia is the most common acquired cause of a bleeding diathesis in children.
- **Pseudothrombocytopenia** Examination of the peripheral blood smear is essential in order to exclude the presence of pseudothrombocytopenia caused by platelet aggregation after using EDTA as an in vitro anticoagulant



- **Prothrombin time (PT)**

- The production of fibrin via the extrinsic pathway and the final common pathway requires tissue thromboplastin (tissue factor), factor VII, factors X, V, prothrombin (factor II), and fibrinogen.
- This test bypasses the intrinsic pathway and uses "complete" thromboplastins (ie, tissue factor) capable of activating the extrinsic pathway.
- The PT is sensitive to alterations in the vitamin K-dependent coagulation factors, especially factors II, VII, and X, and is used to monitor treatment with vitamin K antagonists

- **Activated partial thromboplastin time (aPTT)**
- The aPTT measures the intrinsic and common pathways of coagulation
- This aPTT is routinely used to evaluate intrinsic coagulation and the degree of heparin anticoagulation.
- The aPTT is sensitive to deficiencies of factors XII, XI, IX, and VIII and to inhibitors such as heparin
- It is less sensitive than the PT to deficiencies within the common pathway (eg, factors X, V, prothrombin, and fibrinogen) and is unaffected by alterations in factors VII and XIII.

- **Thrombin Time:**

- Thrombin time measures the final step in the clotting cascade, in which fibrinogen is converted to fibrin.
- The normal thrombin time varies between laboratories ,usually 11-15 sec.
- Prolongation of thrombin time occurs with reduced fibrinogen levels (hypofibrinogenemia or afibrinogenemia), and dysfunctional fibrinogen (dysfibrinogenemia)

- **Bleeding Time**
- Bleeding time assesses the function of platelets and their interaction with the vascular wall
- Bleeding time is a difficult laboratory test to standardize
- **Platelet Function Analyzer:**
- Evaluate the early stages of hemostasis (platelet function and VWF interaction under high shear)
- **The PFA-100** measures platelet adhesion -aggregation in whole blood at high shear when exposed to either collagen-epinephrine or collagen-ADP.
- **Clotting Factor Assays**

Test result		Causes of test result pattern
PT	aPTT	
Prolonged	Normal	<b>Inherited</b>
		Factor VII deficiency
		<b>Acquired</b>
		Mild vitamin K deficiency
		Liver disease
		Warfarin administration*
		Acquired inhibitor of factor VII
Normal	Prolonged	<b>Inherited</b>
		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)
		<b>Acquired</b>
		Heparin administration*
		Inhibitor of factors VIII, IX, XI, or XII
		Acquired von Willebrand disease
		Lupus anticoagulant (may be associated with thrombosis rather than bleeding)

		<b>Inherited</b>
		Deficiency of prothrombin, fibrinogen, or factors V or X
		Combined factor deficiencies
		<b>Acquired</b>
		Liver disease
		Disseminated intravascular coagulation
		Supratherapeutic doses of anticoagulants
		Severe vitamin K deficiency
Prolonged	Prolonged	Combined heparin and warfarin administration
		Direct thrombin inhibitor administration (eg, argatroban, dabigatran)*
		Direct factor Xa inhibitor administration (eg, rivaroxaban, apixaban, edoxaban)
		Inhibitor of prothrombin, fibrinogen, or factors V or X

# Disorders of Platelets

- **Mucocutaneous bleeding** is the hallmark of platelet disorders
- Children with platelet counts less than 20,000/mm<sup>3</sup> are at risk for **spontaneous bleeding**.
- The etiology of thrombocytopenia may be organized into two mechanisms:

1 **Decreased platelet production**

2 **Increased destruction**

# Decreased Platelet Production

## **Thrombocytopenia with absent radii syndrome (TAR):**

- Severe thrombocytopenia in association with orthopedic abnormalities.
- The thrombocytopenia usually improves over time

## **Congenital amegakaryocytic thrombocytopenia (CAMT):**

- Severe thrombocytopenia, but no other congenital anomalies.
- The marrow is devoid of megakaryocytes and usually progresses to aplasia of all hematopoietic cell lines.



# Decreased Platelet Production

- Acquired thrombocytopenia as a result of decreased production is **rarely an isolated finding**.
- It is seen more often in the context of pancytopenia resulting from **bone marrow failure** caused by infiltrative or aplastic processes.

# Peripheral Destruction

## **Immune Thrombocytopenic Purpura**

- Autoimmune thrombocytopenic purpura of childhood (childhood ITP) is a common disorder that usually follows an acute viral infection.
- Childhood ITP is caused by an antibody (IgG or IgM) that binds to the platelet membrane.
- Clinical Manifestations. Young children typically exhibit ITP 1 to 4 weeks after viral illness, with abrupt onset of petechiae, purpura, and epistaxis.

# Immune Thrombocytopenic Purpura

- The thrombocytopenia usually is severe.
  - Significant adenopathy or hepatosplenomegaly is unusual,
  - Red blood cell (RBC) and white blood cell (WBC) counts are normal.
  - The diagnosis of ITP usually is based on clinical presentation and the platelet count and does not often require a bone marrow examination.
- 
- **If atypical findings are noted, however, marrow examination is indicated to rule out an infiltrative disorder (leukemia) or an aplastic process (aplastic anemia).**

# Immune Thrombocytopenic Purpura

- **BM study before steroid treatment**
- Increased megakaryocytes and normal erythroid and myeloid elements.
- Therapy is seldom indicated for platelet counts greater than 30,000/mm<sup>3</sup>.
- Therapy does not affect the long-term outcome of ITP but is intended to increase the platelet count acutely.

- For moderate and severe clinical bleeding with severe thrombocytopenia (platelet count  $<10,000/\text{mm}^3$ )
- Therapeutic options include **prednisone**, 2 to 4 mg/kg/24 hours for 2 weeks or **IVIg**, 1 g/kg/24 hours for 1 to 2 days or **Anti D** Immunoglobulin
- Approximately 80% of children have a spontaneous resolution of ITP within 6 months after diagnosis.
- Serious bleeding, especially intracranial bleeding, occurs in fewer than 1% of patients with ITP.

- ITP that persists for 6 to 12 months is classified as chronic ITP.
- Repeated treatments with IVIG, IV anti-D, or high-dose pulse steroids are effective in delaying the need for splenectomy.
- Rituximab ( anti CD20) induces remission in 50% of cases
- Thrombopoietin agonists

- Secondary causes of chronic ITP, especially SLE and HIV infection, should be ruled out.
- Splenectomy induces a remission in 70% to 80% of childhood chronic ITP cases.
- The risks of splenectomy (surgery, sepsis from encapsulated bacteria) must be weighed against the risk of severe bleeding.

- **Wiskott-Aldrich syndrome**

- Is an X-linked disorder characterized by hypogammaglobinemia, eczema, and thrombocytopenia

- Small platelets are seen on a peripheral blood smear.

- **Hemolytic uremic syndrome** occurs as a result of exposure to a toxin that induces endothelial injury, fibrin deposition, and platelet activation and clearance

- **Thrombotic thrombocytopenic purpura** platelet consumption, precipitated by a congenital or acquired deficiency of a metalloproteinase that cleaves von Willebrand factor.



# Disorders of Platelet Function

- **Primary disorders** of platelet function may involve receptors on platelet membranes for adhesive proteins.
- **Glanzmann thrombasthenia** is an **autosomal recessive** disorder characterized by diminished ability of platelets to aggregate and form a clot as a result of deficient adhesive glycoprotein IIb/IIIa (receptor for fibrinogen) on the platelet cell membrane.

# Disorders of Platelet Function

- **Bernard–Soulier syndrome** is an **autosomal recessive** disorder characterized by decreased platelet adhesion as a result of absence of platelet membrane glycoprotein Ib (receptor for collagen).
- Severe hemorrhage may occur, and large unusual platelets are seen on blood smear.

- **Secondary disorders** caused by toxins and drugs (uremia, valproic acid, aspirin, nonsteroidal anti-inflammatory drugs, and infections)
- Disorders of platelet function present with mucocutaneous bleeding and a prolonged bleeding time or abnormal platelets aggregation

# Disorders of Clotting Factors

- **Congenital clotting factor disorders.** These disorders include deficiency of **factor VIII** and **von Willebrand disease** (both of which are factor VIII–related disorders) and deficiency of **factor IX**.
- **Factor VIII disorders** include two inherited disorders
- **Hemophilia A** represents a defect in factor VIII procoagulant activity and normal Platelet function.

- **von Willebrand disease**
- factor VIII procoagulant activity is variable, but platelet function is defective because of a decrease or defect in **von Willebrand factor**, a protein required for platelet adhesion to blood vessel wall.
- It also functions as a carrier protein for factor VIII.

# Factor VIII deficiency—hemophilia A

- **Inheritance is X-linked** and occurs in 1 in 5000–10,000 male births.  
**Clinical features**
- **Hemarthroses** (involving the knees, elbows, and ankles most commonly) and **deep soft tissue bleeding** are the **hallmarks**.
- **Bleeding into the iliopsoas muscle** may be especially severe as a result of delayed recognition of the bleeding and the potential for significant blood accumulation.

# Factor VIII deficiency—hemophilia A

**Severe, moderate, and mild forms** exist based on the activity level of factor VIII protein.

- **Severe: spontaneous bleeding** (<1% factor VIII protein activity)
- **Moderate: bleeding only with trauma** (1–5% factor VIII protein activity)
- **Mild: bleeding only after surgery or major trauma** (>5% factor VIII protein activity)
- **Central nervous system (CNS) bleeding** is the most dreaded complication and is usually the result of head trauma.

# Factor VIII deficiency—hemophilia A

## Laboratory findings

- **Prolonged aPTT** (in mild form, aPTT may be normal)
- **Normal PT, platelet count, and platelet function assay**
- **Low factor VIII protein activity** in the presence of normal von Willebrand factor assay



# Factor VIII deficiency—hemophilia A

- **Management.** Treatment includes prevention of trauma and replacement of factor VIII.
- Desmopressin acetate (DDAVP) causes the release of stored factor VIII from the patient's own cells and may be useful in mild hemophilia A.

# Von Willebrand disease

- The **most common hereditary bleeding disorder**.
- Inheritance is most commonly **autosomal dominant**.
- **Type I (classic type)**: mild quantitative deficiencies of vWf and factor VIII protein. It is the **most common form**.
- Type II: qualitative abnormality in vWf
- Type III: absence of vWf; the most severe type

# Von Willebrand disease

- **Clinical features**
- **Most patients** have mild to moderate bleeding, usually involving
- mucocutaneous surfaces.
  
- More profound bleeding occurs in type III disease.
  
- **Common signs and symptoms** include epistaxis, **menorrhagia**, bruising, and bleeding after dental extraction or tonsillectomy
  
- **Hemarthroses are unusual.**

# Von Willebrand disease

- **Laboratory findings**
- **Prolonged bleeding time and prolonged aPTT may be present, but not always** (but they are always present in type III disease).
- **Quantitative assay for vWf antigen and activity (ristocetin cofactor assay) are diagnostic.**

# Von Willebrand disease

- **Management. DDAVP** induces vWf release from endothelial cells and is used for mild to moderate bleeding and for prophylaxis before surgery.
- DDAVP is most useful in type I disease and is sometimes effective in type II disease.
- Cryoprecipitate, which contains intact vWf, may be used for serious bleeding, for extensive surgeries, or for type III disease.

## Factor IX deficiency hemophilia B

- This **X-linked disorder** has clinical features similar to those of hemophilia A and occurs in 1 in 50,000 males.
- aPTT is prolonged and low factor IX activity is found.
- PT and platelet count are normal.
- Management includes factor IX replacement.

**Table 151-3** Comparison of Hemophilia A, Hemophilia B, and von Willebrand Disease

FEATURE	HEMOPHILIA A	HEMOPHILIA B	VON WILLEBRAND DISEASE
Inheritance	X-linked	X-linked	Autosomal dominant
Factor deficiency	Factor 8	Factor 9	vWF, factor 8
Bleeding site(s)	Muscle, joint, surgical	Muscle, joint, surgical	Mucous membranes, skin, surgical, menstrual
Prothrombin time	Normal	Normal	Normal
Activated partial thromboplastin time	Prolonged	Prolonged	Prolonged or normal
Bleeding time/PFA-100	Normal	Normal	Prolonged or normal
Factor 8 coagulant activity	Low	Normal	Low or normal
von Willebrand factor antigen	Normal	Normal	Low
von Willebrand factor activity	Normal	Normal	Low
Factor 9	Normal	Low	Normal
Ristocetin-induced platelet agglutination	Normal	Normal	Normal, low, or increased at low-dose ristocetin
Platelet aggregation	Normal	Normal	Normal
Treatment	DDAVP* or recombinant factor 8	Recombinant factor 9	DDAVP* or vWF concentrate

# Acquired clotting factor disorders

- **Vitamin K deficiency**
- A fat-soluble vitamin, is essential for the synthesis of both procoagulant and anticoagulant factors, such as **factors II, VII, IX, and X** and **proteins C and S**.
- **Dietary deficiency is unusual**, except during early infancy.
- Pancreatic insufficiency, biliary obstruction, and prolonged diarrhea may result in diminished ability to absorb vitamin K.



- **Medications** may interfere with vitamin K metabolism (e.g., cephalosporins, rifampin, isoniazid, warfarin).
- **Hemorrhagic disease of the newborn** is the result of vitamin K deficiency.
- It may occur early (within 24 hours after birth), within the first week of life (**classic form**), or late (1–3 months after birth).

## Vitamin K deficiency

- **Clinical features.** Clinical manifestations include bruising, oozing from skin puncture wounds and bleeding into organs.
- **Hemorrhagic disease of the newborn is characterized by serious bleeding in the early and late forms**
- CNS bleeding may occur occasionally.

# Vitamin K deficiency

- **Laboratory findings** include **prolonged aPTT and PT.**
- **Management.** Treatment includes administration of vitamin K.
- **Intramuscular administration of vitamin K after birth prevents hemorrhagic disease of the newborn.**
- In severe disease, fresh-frozen plasma (FFP) may be needed.

# Liver disease

- The liver is the major site of production of most coagulation factors.
- vitamin K– dependent factors most severely affected .
- **Laboratory findings. prolonged PT and aPTT, and thrombocytopenia.**
- **Management.** Treatment includes vitamin K, FFP, and platelets as needed.

# DIC

- The initiating event is clotting that leads to consumption of procoagulant factors and resultant hemorrhage.
- DIC is a secondary phenomenon that occurs in response to local factors (large hemangiomas as seen in Kasabach–Merritt syndrome) and systemic factors (sepsis, hypothermia, malignancy, heat stroke, snakebite, burns).
- **Clinical features.** Signs include cutaneous and internal organ bleeding.

- **Laboratory findings**
- **Thrombocytopenia, prolongation of PT and aPTT, reduction in clotting factors** (especially **fibrinogen** and factors II, V, and VIII), and fragmented and helmet-shaped RBCs on blood smear.
- **Management.** Therapy includes treatment of the underlying cause and transfusions of fibrinogen, FFP.
- Heparin may be useful if the underlying defect cannot be corrected.