Bleeding disorders in children

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Hematopoiesis

• Hematopoiesis begins by 3 weeks of gestation with **erythropoiesis** in the yolk sac. By 2 months’ gestation, the primary site of hematopoiesis migrates to the liver. By 5 to 6 months’ gestation, the process shifts from the liver to the bone marrow.

• During infancy, virtually all marrow cavities are actively hematopoietic and the proportion of hematopoietic to stromal elements is quite high.

• As the child grows, hematopoiesis moves to the central bones of the body (vertebrae, sternum, ribs, and pelvis), and the marrow is gradually replaced with fat.
• The normally high hemoglobin level of the fetus is a result of fetal erythropoietin production in the liver in response to low Po2 in utero.

• Normal life span of The RBC is about 120 days.

• Embryonic hemoglobin's are produced during yolk sac erythropoiesis, then replaced by fetal hemoglobin (hemoglobin F, α2γ2) during the hepatic phase.

• During the third trimester, gamma chain production gradually diminishes, replaced by beta chains, resulting in hemoglobin A (α2β2).
During the first few months of postnatal life, rapid growth, shortened RBC survival, and cessation of erythropoiesis cause a gradual decline in hemoglobin levels, with a nadir at 8 to 10 weeks of life.

This so-called physiologic nadir is accentuated in premature infants.

By 6 months of age in healthy infants, only trace gamma chain synthesis occurs.
• Production of neutrophil precursors is controlled predominantly by two different colony-stimulating factors.

• The most immature neutrophil precursors are controlled by granulocyte-macrophage colony-stimulating factor (GM-CSF), produced by monocytes and lymphocytes.

• Granulocyte colony-stimulating factor (G-CSF) augments the production of more mature granulocyte precursors.

• The rapid increase in neutrophil count that occurs with infection is caused by release of stored neutrophils from the bone marrow, under the control of GM-CSF.
• Neutrophils migrate from the bone marrow, circulate for 6 to 7 hours, and enter the tissues, where they become end-stage cells that do not recirculate.

• Eosinophil production is under the control of a related glycoprotein hormone, interleukin 3. Eosinophils, which play a role in host defense against parasites, also are capable of living in tissues for prolonged periods.

• The bone marrow is the major storage organ for mature neutrophils and contains about seven times the intravascular pool of neutrophils.

• It contains 2.5 to 5 times as many cells of myeloid lineage as cells of erythroid lineage. Smaller numbers of megakaryocytes, plasma cells, histiocytes, lymphocytes, and stromal cells are also stored in the marrow.
Megakaryocytes are giant, multinucleated cells derived from the primitive stem cell and are polyploid (16 to 32 times the normal DNA content).

Thrombopoietin is the primary regulator of platelet production. Platelets adhere to damaged endothelium and subendothelial surfaces via specific receptors for the adhesive proteins, von Willebrand factor (vWF), and fibrinogen.

Platelets also have specific granules that readily release their contents after stimulation and trigger the process of platelet aggregation.

Platelets circulate for 7 to 10 days and have no nucleus.
Activated by internal damaged surface

**INTRINSIC PATHWAY**

- XII → XIIα
  - XI → XIα
    - IX → IXα
      - VIII → VIIIα
        - X → Xα
          - Prothrombin (II)

Activated by TISSUE FACTOR

**EXTRINSIC PATHWAY**

- VIIα → VII
  - Tissue factor released due to vascular injury

**COMMON PATHWAY**

- Xa
  - Fibrinogen (I)

Activated by thrombin

- Va
  - Fibrin (Ia)

**CLOT**
Functional Classification of Bleeding Disorders

• Abnormal vessels
  Ehler Danlos
  HSP

• Defects of platelets
  Number: Infection, ITP, Leukemia
  Function: vWD, BS, GT, Drugs

• Abnormal coagulation
  Congenial: Hemophilia A or B
  Acquired: Liver disease, Vit K def, DIC
## Bleeding Disorders

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Primary hemostasis</th>
<th>Secondary hemostasis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Onset</td>
<td>Spontaneous and immediate</td>
<td>Delayed after trauma</td>
</tr>
<tr>
<td>Usual site</td>
<td>Skin, mucous membranes</td>
<td>Deep tissues / hemarthrosis</td>
</tr>
<tr>
<td>Other sites</td>
<td>Rare</td>
<td>Retroperitoneum, CNS</td>
</tr>
<tr>
<td>Examples</td>
<td>Thrombocytopenia, platelet defects (vWD)</td>
<td>Factor deficiency or inhibitor</td>
</tr>
<tr>
<td>Clinical findings</td>
<td>Disorders of coagulation*</td>
<td>Purpuric disorders *</td>
</tr>
<tr>
<td>--------------------------------</td>
<td>---------------------------</td>
<td>----------------------</td>
</tr>
<tr>
<td>Skin - petechiae</td>
<td>Not usually seen</td>
<td>Characteristic</td>
</tr>
<tr>
<td>Ecchymosis</td>
<td>Common - large one or more</td>
<td>Characteristic - small or many scattered</td>
</tr>
<tr>
<td>Soft tissue hematoma</td>
<td>Characteristic</td>
<td>Rare</td>
</tr>
<tr>
<td>Joint hemorrhages</td>
<td>Characteristic - hallmark of the disease</td>
<td>Not usually seen</td>
</tr>
<tr>
<td>Delayed bleeding</td>
<td>Common</td>
<td>Rare</td>
</tr>
<tr>
<td>Bleeding from superficial skin abrasions</td>
<td>Uncommon</td>
<td>Common and persistent</td>
</tr>
<tr>
<td>Family history of bleeding</td>
<td>Common</td>
<td>Rare</td>
</tr>
<tr>
<td>Sex of the patient</td>
<td>Predominantly male</td>
<td>Predominantly female</td>
</tr>
</tbody>
</table>
History:

Neonatal bleeding
Bleeding after circumcision
Delayed bleeding from umbilical stump (factor XIII)
Deep hematoma after I.M injections
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
Telangietic vessels
Hemangiomases
Loose joints and lax skin associated with easy bruising (Ehlers-Danlos syndrome)
Diagnosis of Coagulation Disorders Screening Tests

- Complete blood count:

- Thrombocytopenia when less than 150,000/mm³
- Platelet count is essential in the evaluation of the child with a positive bleeding history because thrombocytopenia is the most common acquired cause of a bleeding diathesis in children.
- Pseudothrombocytopenia Examination of the peripheral blood smear is essential in patients with low platelet counts 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 but is 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.

  - Results are reported as the closure time measured in sec.

• **Clotting Factor Assays:**
<table>
<thead>
<tr>
<th>Test result</th>
<th>Causes of test result pattern</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>PT</strong></td>
<td><strong>aPTT</strong></td>
</tr>
<tr>
<td>Prolonged</td>
<td>Normal</td>
</tr>
<tr>
<td>Inherited</td>
<td></td>
</tr>
<tr>
<td>Factor VII deficiency</td>
<td></td>
</tr>
<tr>
<td>Acquired</td>
<td></td>
</tr>
<tr>
<td>Mild vitamin K deficiency</td>
<td></td>
</tr>
<tr>
<td>Liver disease</td>
<td></td>
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<tr>
<td>Warfarin administration*</td>
<td></td>
</tr>
<tr>
<td>Acquired inhibitor of factor VII</td>
<td></td>
</tr>
<tr>
<td>Normal</td>
<td>Prolonged</td>
</tr>
<tr>
<td>Inherited</td>
<td></td>
</tr>
<tr>
<td>Deficiency of factors VIII, IX, or XI</td>
<td></td>
</tr>
<tr>
<td>Deficiency of factor XII, prekallikrein, or HMW kininogen (not associated with a bleeding diathesis)</td>
<td></td>
</tr>
<tr>
<td>von Willebrand disease (variable)</td>
<td></td>
</tr>
<tr>
<td>Acquired</td>
<td></td>
</tr>
<tr>
<td>Heparin administration*</td>
<td></td>
</tr>
<tr>
<td>Inhibitor of factors VIII, IX, XI, or XII</td>
<td></td>
</tr>
<tr>
<td>Acquired von Willebrand disease</td>
<td></td>
</tr>
<tr>
<td>Lupus anticoagulant (may be associated with thrombosis rather than bleeding)</td>
<td></td>
</tr>
<tr>
<td>Prolonged</td>
<td>Prolonged</td>
</tr>
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<td>-----------</td>
<td>-----------</td>
</tr>
<tr>
<td><strong>Inherited</strong></td>
<td></td>
</tr>
<tr>
<td>Deficiency of prothrombin, fibrinogen, or factors V or X</td>
<td></td>
</tr>
<tr>
<td>Combined factor deficiencies</td>
<td></td>
</tr>
<tr>
<td><strong>Acquired</strong></td>
<td></td>
</tr>
<tr>
<td>Liver disease</td>
<td></td>
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<tr>
<td>Disseminated intravascular coagulation</td>
<td></td>
</tr>
<tr>
<td>Supratherapeutic doses of anticoagulants</td>
<td></td>
</tr>
<tr>
<td>Severe vitamin K deficiency</td>
<td></td>
</tr>
<tr>
<td>Combined heparin and warfarin administration</td>
<td></td>
</tr>
<tr>
<td>Direct thrombin inhibitor administration (eg, argatroban, dabigatran)*</td>
<td></td>
</tr>
<tr>
<td>Direct factor Xa inhibitor administration (eg, rivaroxaban, apixaban, edoxaban)</td>
<td></td>
</tr>
<tr>
<td>Inhibitor of prothrombin, fibrinogen, or factors V or X</td>
<td></td>
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Disorders of Platelets

• **Mucocutaneous bleeding** is the hallmark of platelet disorders

• Children with platelet counts less than 20,000/mm$^3$ 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/mm³.

• 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/mm3)

• 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 hypogammaglobulinemia, 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>
<thead>
<tr>
<th>FEATURE</th>
<th>HEMOPHILIA A</th>
<th>HEMOPHILIA B</th>
<th>VON WILLEBRAND DISEASE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inheritance</td>
<td>X-linked</td>
<td>X-linked</td>
<td>Autosomal dominant</td>
</tr>
<tr>
<td>Factor deficiency</td>
<td>Factor 8</td>
<td>Factor 9</td>
<td>vWF, factor 8</td>
</tr>
<tr>
<td>Bleeding site(s)</td>
<td>Muscle, joint, surgical</td>
<td>Muscle, joint, surgical</td>
<td>Mucous membranes, skin, surgical, menstrual</td>
</tr>
<tr>
<td>Prothrombin time</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
</tr>
<tr>
<td>Activated partial thromboplastin time</td>
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<td>Prolonged</td>
<td>Prolonged or normal</td>
</tr>
<tr>
<td>Bleeding time/PFA-100</td>
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<td>Prolonged or normal</td>
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<td>Factor 8 coagulant activity</td>
<td>Low</td>
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<td>Low or normal</td>
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<tr>
<td>von Willebrand factor antigen</td>
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<tr>
<td>von Willebrand factor activity</td>
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<td>Factor 9</td>
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<td>Low</td>
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<tr>
<td>Ristocetin-induced platelet agglutination</td>
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<td>Normal</td>
<td>Normal, low, or increased at low-dose ristocetin</td>
</tr>
<tr>
<td>Platelet aggregation</td>
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<td>Normal</td>
<td>Normal</td>
</tr>
<tr>
<td>Treatment</td>
<td>DDAVP* or recombinant factor 8</td>
<td>Recombinant factor 9</td>
<td>DDAVP* or vWF concentrate</td>
</tr>
</tbody>
</table>
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 (e.g., large hemangiomas as seen in Kasabach–Merritt syndrome) and systemic factors (e.g., 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, and platelets as needed. Heparin may be useful if the underlying defect cannot be corrected.