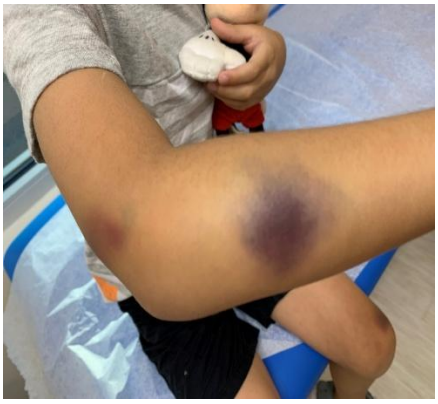
Pediatric Hematology-Handout

Normal CBC and CBC interpretation

IgA Vasculitis

Normal CBC

Immune Thrombocytopenia (ITP)



Normal except platelets
7000 /cells/mm^3

Leukemia

Low or high WBCs
Anemia
Platelets **20000 /cells/mm^3**

Anemia

RBCs

Anemia

Pathophysiology

Decreased production

- Deficiency: Iron, Folic acid, B12
- Infiltration: Leukemia, lymphoma
- Bone marrow failure or toxins

Increased destruction

- Defective hemoglobin: Thalassemia
- Membrane defect: Spherocytosis
- Enzyme deficiency: G6PD
- Autoimmune

Clinical Case

An 8-week-old with hemoglobin **11 g/dL**, normal MCV for age, a reticulocyte count of **0.4%**, normal direct and indirect bilirubin levels, and a negative direct antibody test.
The infant's hemoglobin was **15.8 g/dL at birth**.
No symptoms.

What is the most likely cause of hemoglobin drop?

Physiologic anemia of infancy

Physiologic Anemia of Infancy

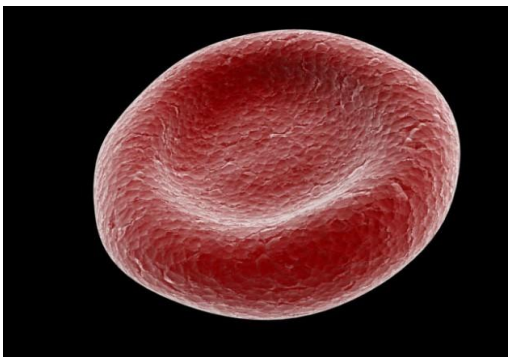
Nadir

- **9–11 g/dL** — physiologic anemia of infancy
- Frequent phlebotomies may exacerbate the physiologic anemia
- Oxygen and adult hemoglobin → ↓ erythropoietin production
- Occurs at:
    - **8–12 weeks** (term)
    - **3–8 weeks** (preterm)

- Self-limited and will resolve by **3-6 months**

Board Pearl:
Low reticulocyte count with normal bilirubin in early infancy strongly supports physiologic anemia.

Classification of Anemia by MCV



Age > 1 year

- **Microcytic:** MCV < (70 + age) fL
- **Normocytic:** MCV ≥ (70 + age) and <100 fL
- **Macrocytic:** MCV >100 fL

Microcytic Anemia

Components

Hemoglobin
→ Heme + Globin

Heme
→ Iron + Protoporphyrin

Causes

- Iron deficiency anemia
- Anemia of chronic disease

- Thalassemia
- Sideroblastic anemia

Clinical Case

A 3-year-old boy with pallor.
Drinks **32–40 oz of cow's milk/day**.
No jaundice, no hepatosplenomegaly, no lymphadenopathy.

Labs

- WBC: 7,500 /µL
- RBC: 4 million /mm^3
- Hemoglobin: **6.0 g/dL**
- MCV: **59 fL**
- Platelets: **495,000 ×10^3/µL**
- Reticulocyte count: **0.3%**

Diagnosis: Iron deficiency anemia

Mentzer index

- 59 / 4 = **14.75** (>13)

Board Pearl:
Excessive cow's milk intake is a classic risk factor for iron deficiency anemia in toddlers.

Iron Deficiency Anemia (IDA)

Etiology – Nutritional

- Exclusive breastfeeding (iron supplementation recommended from **4 months**)
- Lack of iron-rich foods
- Excessive cow's milk intake (>24 oz/day)
  → direct intestinal injury
- Impaired absorption

- Malabsorption (iron absorbed from duodenum)
- Celiac disease

Etiology – Blood Loss

Gastrointestinal

- Cow's milk allergy
- Exudative enteropathy
- Meckel's diverticulum
- Vascular malformations
- Hookworms

Genitourinary

- Menstrual
- Hemoglobinuria

Pulmonary

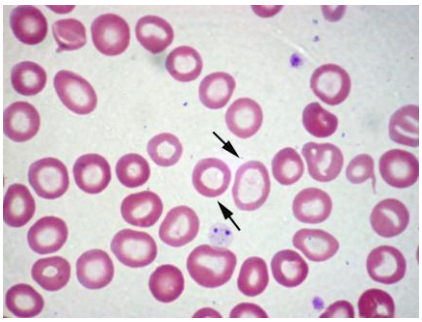
- Goodpasture syndrome
- Pulmonary hemosiderosis

Clinical Presentation

- Pallor
- Koilonychia
- PICA (ice, dirt)
- Headache
- Irritability
- Poor academic performance
- Anorexia
- Tachycardia

- Systolic murmur

Laboratory Findings



- Low MCV → microcytic
- Low MCHC
- Elevated platelet count (>450,000 /µL)
- Normal or elevated WBC
- Can be normocytic early
- Target cells usually **not present**

Iron Studies

- Low serum iron
- **Low ferritin level**
    - Ferritin ≤20 ng/mL (children ≤10 years)
    - Ferritin ≤30 ng/mL (age ≥11 years)
- Low reticulocyte count
- Elevated TIBC
- Elevated soluble transferrin receptor (sTfR)
- Mentzer index >13

Note:
Normal ferritin can be seen with coexistent inflammation.

Treatment

- Oral ferrous salts
- **2–3 mg/kg/day elemental iron**
- Side effects: taste, GI irritation, constipation

Enhance absorption

- Give on empty stomach
- With orange juice or lemonade

Monitoring Response

- Repeat CBC in **4 weeks**
- Hemoglobin rises **≥1 g/dL in 14 days**
- Continue iron therapy **3 months after correction**

Transfusion Indications

- Hemoglobin **<5 g/dL**
- Or signs of distress (tachycardia, lethargy, respiratory distress)

Dose

- **5 mL/kg over 4 hours**
- Transfuse slowly to avoid CHF

Prevention

- Preterm infants: **2 mg/kg/day** iron by 1 month
- Full-term: **1 mg/kg/day** from 4 months
- No whole milk before **12 months**
- Limit excessive milk intake

Board Pearl:
A hemoglobin rise after iron therapy is both diagnostic and therapeutic.

Sideroblastic Anemia

Pathophysiology

Defective **protoporphyrin synthesis in mitochondria**

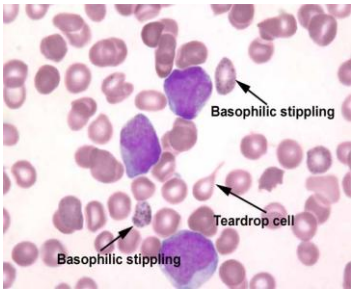
Causes

- Congenital (ALAS mutation)
- Lead poisoning
- Vitamin B6 deficiency (isoniazid)
- Pearson marrow-pancreas syndrome

Laboratory Features

- Microcytic (or normocytic) anemia
- Ringed sideroblasts in bone marrow
- Ineffective erythropoiesis
- Mild to moderate hemolysis
- Risk of acute leukemia

Lead Poisoning



- High serum lead

- Elevated free erythrocyte protoporphyrin
- Basophilic stippling

Treatment

- Lead 45–69 µg/dL → **Succimer (oral)**
- Lead ≥70 µg/dL → **Hospitalization**

Thalassemia

- Normal iron studies
- Normal FEP
- Mentzer index **<13**

Free Erythrocyte Protoporphyrin (FEP)

- **Elevated:** Iron deficiency anemia, lead poisoning
- **Normal:** Thalassemia

Board Pearl:
FEP helps distinguish iron deficiency from thalassemia.

Anemia of Chronic Disease

Associations

- Chronic systemic diseases
- Chronic inflammatory process; e.g., SLE
- Chronic pyogenic infection

Etiology

- Releases of inflammatory cytokines:
    - IL-6
    - IL-1

    - TNF
- Hepcidin released from the liver:
    - Decreases intestinal iron absorption
    - Blocks release of iron from macrophages

Board Pearl:
Hepcidin is the key mediator linking inflammation to impaired iron utilization.

Laboratory

- Low hemoglobin concentration (usually **6–9 g/dL**)
- Low MCV (can be normocytic in the beginning)
- Often normochromic anemia with progression to hypochromia
- Low serum iron
- Elevated serum ferritin
- Low TIBC

Board Pearl:
Elevated ferritin distinguishes anemia of chronic disease from iron deficiency anemia.

Treatment

- Treatment of the cause
- Recombinant EPO may increase the hemoglobin level and improve well-being in patients with cancer

Board Pearl:

Iron therapy alone is ineffective unless inflammation is controlled.

Thalassemia

- Decrease production of alpha or beta globin

Normal Hemoglobin Types

- HbF ($\alpha_2 \gamma_2$)
- HbA ($\alpha_2 \beta_2$)
- HbA_2 ($\alpha_2 \delta_2$)

(α and non-α) pair **1:1 ratio**

Excess of normally produced type → cell destruction

Board Pearl:
Imbalance of globin chain production causes ineffective erythropoiesis.

Alpha Thalassemia

Gene Deletions

- 1 gene deletion
- 2 gene deletion
- 3 gene deletion
- 4 gene deletion
- Cis deletion
- Trans deletion

Chromosome **16**

Silent Trait

- Deletion or dysfunction of **one gene**
- Asymptomatic
- 1–2% Hgb Barts on neonatal electrophoresis
- Normal hemoglobin electrophoresis

Alpha Thalassemia Trait

- Deletion or dysfunction of **two genes**
- Mild hypochromic microcytic anemia
- 3–10% Hgb Barts on neonatal electrophoresis
- Mentzer Index <13
- Hgb >9 g/dL
- Normal hemoglobin electrophoresis
- Often misdiagnosed as iron deficiency anemia

Board Pearl:
Iron therapy does not improve thalassemia trait.

Hemoglobin H Disease

- Deletion of **three genes**
- Mild to moderate hypochromic microcytic anemia
- Splenomegaly
- Jaundice
- Cholelithiasis (pigment stones)
- Anemia exaggerated by infection, pregnancy, oxidizing drugs
- 25% Hgb Barts on neonatal electrophoresis

Alpha Thalassemia Major

- Deletion of **four genes**
- Fetal hydrops
- Fatal disease
- Predominant Hgb Barts

Board Pearl:
Hydrops fetalis with no HbA suggests alpha-thalassemia major.

Beta Thalassemia

- Due to gene mutation
- Chromosome **11**

Variants

- β^+
- β^0
- β/β^+
- β^0/β^0

Beta Thalassemia Minor

- Slight decrease in HbA
- Increased HbA_2 >3.5%
- Increased HbF to ~2%
- Usually asymptomatic

Beta Thalassemia Major (Cooley's Anemia)

- Little or no HbA
- Increased HbA_2 and HbF
- Ineffective erythropoiesis
- Increased destruction of RBCs
- Excess alpha globin chains
- Shortened RBC lifespan and splenic trapping

Board Pearl:
Absence of HbA is diagnostic of beta-thalassemia major.

Clinical Presentation

- Severe anemia
- Pallor
- Jaundice
- Fatigue
- Hepatosplenomegaly

Skeletal

- Maxillary hyperplasia
- Flat nasal bridge
- Frontal bossing
- Pathologic fractures

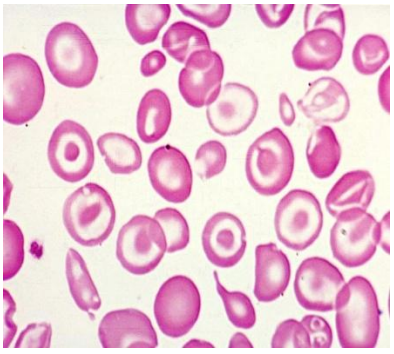
Endocrine

- Hypothyroidism
- Hypoparathyroidism
- Diabetes mellitus

Cardiovascular

- Congestive heart failure

Laboratory



- Severe anemia
- Few reticulocytes (<8%)

- Microcytosis with **no normal RBCs**
- Numerous nucleated RBCs
- Target cells
- Mentzer index:
    - <13 → thalassemia trait
    - <9 → thalassemia major
- Elevated indirect bilirubin

Treatment

- Long-term transfusion therapy
- Iron chelation:
    - Deferoxamine IV
    - Deferiprone oral
- Splenectomy
- Allogeneic hematopoietic transplantation
- Gene therapies
- Supportive measures

Beta Thalassemia Trait

- No treatment required
- Iron will not improve anemia
- Iron **only if** iron deficiency occurs

Board Pearl:
Do not give iron unless iron deficiency is proven.

Macrocytic Anemia (MCV >100)

Non-Megaloblastic

- Liver disease
- Hypothyroidism

Megaloblastic

- Folic acid deficiency
- Vitamin B12 deficiency

Folic Acid Deficiency

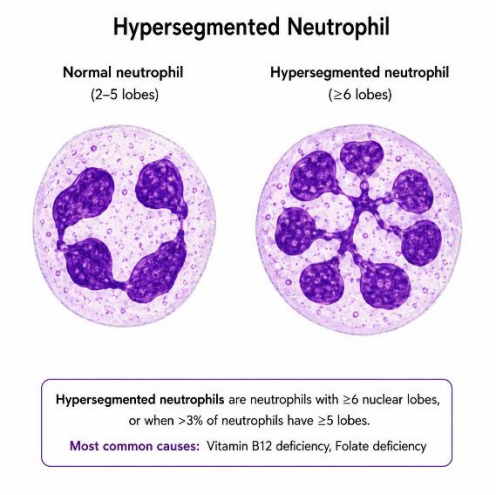
Etiology

- Nutritional deficiency
- Increased demand (pregnancy, growth, hemolysis)
- Goat milk consumption
- Ileal disease or resection
- Anticonvulsants
- Methotrexate

Clinical Presentation

- Megaloblastic anemia
- Glossitis
- Irritability
- Poor weight gain
- Diarrhea
- Thrombocytopenia in severe cases

Laboratory



- Macrocytic anemia
- Hypersegmented neutrophils
- Elevated LDH
- Low serum folate
- High homocysteine

Treatment

- Rule out B12 deficiency first
- Folic acid 0.5–1 mg/day
- Hematologic response within 72 hours
- Maintenance dose 0.2 mg daily

Board Pearl:
Treating B12 deficiency with folate alone worsens neurologic injury.

Vitamin B12 Deficiency

Etiology

- Strict vegan diet
- Exclusively breastfed infant with maternal vegan diet

- Terminal ileum disease or resection
- Fish tapeworm
- Absence of intrinsic factor

Neurologic Symptoms

- Subacute combined degeneration
- Ataxia
- Paresthesias
- Developmental regression

Laboratory

- Macrocytic anemia
- Hypersegmented neutrophils
- Elevated LDH
- Increased methylmalonic acid
- Increased homocysteine
- Low reticulocyte count

Treatment

- Parenteral vitamin B12
- Continue ≥2 weeks if neurologic symptoms
- Monthly IM for life if pernicious anemia

Board Pearl:
Neurologic symptoms may be irreversible if treatment is delayed.

Pearson marrow-pancreas syndrome

Know that

- Pearson syndrome is a variant of **sideroblastic anemia**

Clinical presentation

- Macrocytic anemia in neonatal period
- Elevated level of alpha-feto protein
- Neutropenia
- Thrombocytopenia
- Failure to thrive

Clinical Presentation

- Insulin dependent diabetes mellitus
- Exocrine pancreatic deficiency
- Muscle and neurologic impairment

Laboratory

- Bone marrow
    - Ringed sideroblast
    - Vacuolated erythroblast and myeloblast

Schwachman-Diamond Syndrome

Genetics

- Autosomal recessive

Clinical Presentation

- Failure to thrive
- Exocrine pancreatic insufficiency – **50%**
- Fat malabsorption
- Skeletal abnormalities
- Short stature

- Abnormal digits:
    - Syndactyly
    - Clinodactyly
- Neutropenia or pancytopenia + pancreatic dysfunction

Schwachman-Diamond Syndrome

Clinical Presentation (continued)

- Abnormal facies
- Bifid uvula or cleft palate
- Dental dysplasia
- Hypertelorism
- Microcephaly
- Retinitis pigmentosa
- Recurrent bacterial infections

Schwachman-Diamond Syndrome

Laboratory

- Abnormal pancreatic enzymes
- Steatorrhea
- Neutropenia
- Bone marrow showing myeloid hypoplasia
- Pancytopenia – **60%**

Diagnosis

- Mutation analysis for **SBDS** gene is definitive in **90%**

Schwachman-Diamond Syndrome

Complications

- Increase with age (usually after 10 years):
    - Aplastic anemia
    - Myelodysplastic syndrome
    - Acute myelogenous leukemia

Treatment

- G-CSF can improve neutropenia
    - May accelerate risk of myeloproliferative disorders
- Pancreatic enzymes
- Fat-soluble vitamins
- Androgen with low dose prednisone

Board Pearl:
Schwachman-Diamond syndrome has increasing leukemia risk with age.
Neutropenia plus pancreatic dysfunction is classic for Schwachman-Diamond syndrome

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Diamond-Blackfan Anemia

- Congenital hypoplastic anemia
- Primary defect in erythroid progenitors

Clinical Presentation

- Severe anemia by 2–6 months
- Congenital anomalies:
    - Snub nose
    - Wide-set eyes
    - Thick upper lip
    - Triphalangeal thumbs

Laboratory

- Macrocytic RBCs
- No hypersegmented neutrophils
- Elevated ADA
- Low reticulocytes
- Normal chromosomes

Treatment

- Steroids
- Iron chelation if transfusion dependent
- Stem cell transplant if refractory

Fanconi Anemia

Genetics

- Autosomal recessive
- Mutation in **FANCA and FANCC genes**

Fanconi Anemia

Clinical Presentation

Fanconi anemia

- Skin abnormalities in **65%** of cases:
    - Hyperpigmentation of trunk and intertriginous areas
    - Café-au-lait spots
    - Vitiligo
- Short stature – **60%**
- Upper limb anomalies – **50%**
    - Absent thumb
    - Triphalangeal thumb
- Congenital hip dysplasia

Fanconi Anemia

Clinical Presentation (continued)

- Genital anomalies
- Facial anomalies:
    - Microcephaly
    - Small eyes
    - Epicanthal folds
    - Abnormal shape ears or absent ears
- Intellectual disability – **10%**
- Kidney abnormalities:
    - Horseshoe kidney
    - Absent or duplicate kidney

Fanconi Anemia

- Anemia (macrocytic)
- Pancytopenia

- Microcephaly
- Café-au-lait spots
- Short stature
- Triphalangeal thumbs or absent thumb
- Intellectual disability

Board Pearl:
Fanconi anemia affects **all blood cell lines**.
Pancytopenia with skeletal abnormalities strongly suggests Fanconi anemia.

Fanconi Anemia

Laboratory

- Macrocytic anemia
- Variable progression to full-blown pancytopenia due to aplasia
- Diepoxybutane (DEB) DNA analysis

Complications

- Acute leukemia
- Carcinoma of head and neck and upper esophagus

Board Pearl:
Fanconi anemia carries a high risk of leukemia and solid tumors.

Transient Erythroblastopenia of Childhood

- Most common acquired red cell aplasia
- Age: **3 months–3 years**
- Triggered by viral infection
- No Parvovirus B19

Laboratory

- Normal MCV

- Low reticulocytes
- Normal ADA

Treatment

- Reassurance
- Recovery in 2–3 months
- Transfusion rarely required

Board Pearl:
Normal ADA distinguishes TEC from Diamond-Blackfan anemia.

Transient Erythroblastopenia of Childhood (TEC) ***(Acquired Pure Red Cell Aplasia)***	**Diamond-Blackfan Anemia (DBA)** ***(Congenital Pure Red Cell Aplasia)***
Age at presentation: 1–3 years (most common)	**Age at presentation:** 2–3 months
Frequency: Common	**Frequency:** Extremely rare
MCV: Normocytic (normal MCV)	**MCV:** Macrocytic
Reticulocyte count: Low	**Reticulocyte count:** Low
Serum iron: Normal	**Serum iron:** Increased
Congenital anomalies: Absent	**Congenital anomalies:** Present in ~50% (e.g., craniofacial, thumb, cardiac abnormalities)
Bone marrow: Isolated erythroid hypoplasia	**Bone marrow:** Marked erythroid hypoplasia/aplasia
Treatment: Usually observation; transfusion rarely required	**Treatment:** Blood transfusions often required; corticosteroids are first-line therapy after infancy. Hematopoietic stem cell transplantation is curative for selected patients.

Hemolytic Anemia

- Reticulocytosis
- Jaundice
- Anemia

Anemia with Reticulocytosis

- Peripheral smear changes:
    - Spherocytes → spherocytosis
    - Spherocytes + positive Coombs test → autoimmune hemolytic anemia
    - Sickle cells → sickle cell anemia
    - Bite cells and Heinz bodies → G6PD
    - Schistocytes + abnormal renal function → HUS
- "Classic triad"
    - LDH
    - Indirect bilirubin
    - Haptoglobin

Board Pearl:
Elevated LDH + indirect bilirubin + low haptoglobin confirms hemolysis.

Reticulocyte Count

- Normal retic count:
    - Full-term infants: **3–7**
    - Pre-term infants: **5–10**
    - Infants and children >6 months: **0.5–1**
- Corrected reticulocyte count (CRC):
    - CRC = % Retic × patient HCT / Normal HCT

- CRC >1.5 → suggest hemolysis or blood loss
- Anemia
- False high retic count %
- Example:
    - Retic count: **4%**
    - HCT: **25%**
    - CRC = 4 × 25 / 45 = **2.2%**

Board Pearl:
Always calculate the corrected reticulocyte count to accurately assess marrow response.

Hemolytic Anemia — Mechanism

Intravascular Hemolysis

- Hemolysis within blood vessels
- Hemoglobin + haptoglobin
- ↓ haptoglobin
- Hemoglobinemia
- Hemoglobinuria

Extravascular Hemolysis

- Hemolysis by macrophages in:
    - Spleen
    - Liver
    - Lymph nodes
- Splenomegaly

Board Pearl:
Hemoglobinuria = intravascular hemolysis; splenomegaly = extravascular hemolysis.

Hereditary Spherocytosis

- Autosomal dominant inheritance

Pathophysiology

- Spectrin deficiency
- Spectrin and ankyrin deficiency
- Band 3 deficiency
- Protein 4.2 defects
- Spherical RBCs
- Splenomegaly
- Loss of biconcave shape

Hereditary Spherocytosis — Clinical Presentation

- May be asymptomatic into adulthood
- Anemia
- Pallor
- Jaundice
- Pigment gallstones (as early as 4–5 years)
- Fatigue
- Exercise intolerance
- Splenomegaly

Aplastic Crisis

- Parvovirus B19 infection
- Profound anemia
- HCT <10%
- High cardiac output failure
- Hypoxia

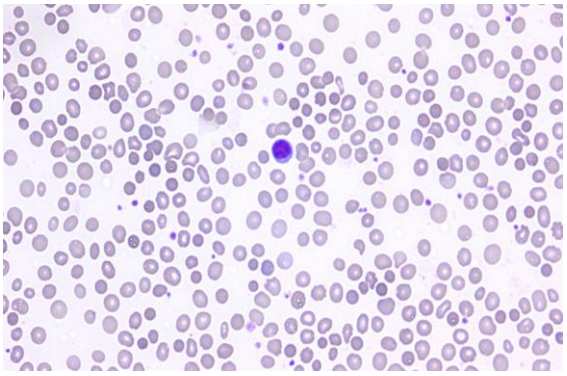
- Cardiovascular collapse and death

Board Pearl:
Sudden severe anemia in hereditary spherocytosis → think parvovirus B19–induced aplastic crisis.

Hereditary Spherocytosis — Laboratory

- Reticulocytosis
- Indirect hyperbilirubinemia
- High LDH
- Low haptoglobin
- Normal MCV
- Elevated MCHC
- High percentage of spherocytes on smear with loss of central pallor
- **Confirmed with:**
    - EMA (eosin-5-maleimide) binding flow cytometry

Note: Osmotic fragility test is less sensitive than EMA flow cytometry



- RBCs:
    - Small
    - Hyperchromatic
    - No central pallor

Board Pearl:
Elevated MCHC is a classic laboratory clue for hereditary spherocytosis.

Hereditary Spherocytosis — Treatment

- Folic acid **1 mg PO daily**

Splenectomy Indications

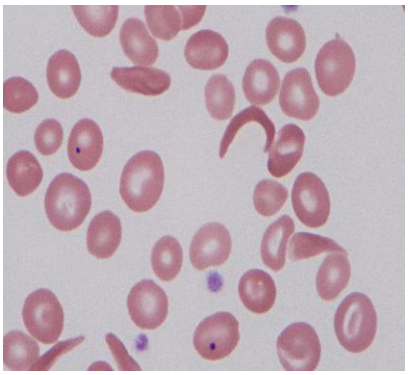
- Hgb <10 g/dL
- Reticulocytosis
- Aplastic crisis
- Poor growth
- Cardiomegaly
- Some do not recommend splenectomy if:
    - Hemoglobin >10 g/dL
    - Reticulocytes <10%

Hereditary Spherocytosis — Post-Splenectomy Care

- Vaccination against encapsulated organisms:
    - Hemophilus influenza
    - Meningococcus
    - Pneumococcus
- Prophylactic penicillin V:
    - <5 years: **125 mg BID**
    - 5 years: **250 mg BID**
- Partial splenectomy useful in children <5 years

Board Pearl:
Vaccination and antibiotic prophylaxis are mandatory after splenectomy.

Howell-Jolly Bodies



- Large
- Single inclusions
- Eccentrically placed

Board Pearl:
Howell-Jolly bodies indicate functional or anatomic asplenia.

Paroxysmal Nocturnal Hemoglobinuria (PNH)

- Acquired disorder
- Hematopoietic cell mutation
- All blood cells affected

Pathophysiology

- GPI anchor defect
- Deficient proteins:
    - MIRL (CD59)
    - DAF (CD55)
- Complement activation
- Intravascular hemolysis
- Sleep → acidosis

Consequences

- Hemoglobinemia
- Hemoglobinuria
- Hemosiderinuria
- Thrombosis
- Pancytopenia
- Most common cause of death:
    - Thrombosis of hepatic, portal, or cerebral veins

PNH — Clinical Presentation

- Nocturnal and morning hemoglobinuria
- Thrombosis and thromboembolic events
- Aplastic anemia may precede PNH

Board Pearl:
Thrombosis is the leading cause of mortality in PNH.

PNH — Laboratory

- RBC elongation, rod-shaped cells
- Evidence of hemolysis:
    - Elevated LDH
    - Elevated bilirubin
    - Low haptoglobin
- Negative direct antiglobulin test
- Flow cytometry:
    - CD55
    - CD59
- Decreased acetylcholinesterase activity

PNH — Treatment

- Acute:
    - Blood transfusion
    - Glucocorticoids **2 mg/kg/24 hours** (controversial)
- Chronic:
    - **Ravulizumab**
    - Warfarin to prevent thrombosis
    - Supplemental iron if needed

Board Pearl:
Flow cytometry showing CD55/CD59 deficiency confirms PNH.

Keywords & Summary — Paroxysmal Nocturnal Hemoglobinuria

- Presence of complement-mediated red destruction
- Deficiency of certain surface proteins on blood cells:
    - Decay-accelerating factor
    - C8 binding protein
- Presents with dark urine and hemoglobinuria at night and in the morning
- Flow cytometry for CD55 and CD59 will confirm the diagnosis
- Treatment of acute attacks:
    - Blood transfusion
    - Corticosteroids

Board Pearl:
Complement-mediated hemolysis with negative Coombs test is classic for PNH.

Sickle Cell Anemia

Background

- Hemoglobin S due to mutation

- Involves substitution of **valine for glutamic acid** at 6th position in beta globin chain
- Autosomal recessive inheritance
- Valine at 6th position instead of normal glutamic acid
- Mutation on chromosome **11**

Sickle Cell Anemia — Pathophysiology

- HbS polymerizes when deoxygenated
- Aggregate → needle-like structures

Triggers

- Hypoxemia
- Dehydration
- Acidosis
- HbF:
    - Protective in the first few months of life
- Extravascular and intravascular hemolysis
- Anemia
- Jaundice (unconjugated)
- Increased risk of gall bladder stones
- Decreased haptoglobin
- Target cells
- Extramedullary hematopoiesis
- Irreversible sickling
- Vaso-occlusion
- Complications:
    - Dactylitis
    - Auto-splenectomy

    - Acute chest syndrome
    - Pain crisis
    - Renal papillary necrosis

Board Pearl:
Deoxygenation triggers HbS polymerization and vaso-occlusion.

Sickle Cell Anemia — Clinical Presentation

- Usually diagnosed on neonatal screen
- Manifestations can be as early as **6 months of age**

Crisis

- Splenic sequestration
- Pain crisis
- Aplastic crisis
    - Parvovirus B19 is a frequent cause

Sickle Cell Anemia — Infections

- Bacterial sepsis is the greatest cause of morbidity and mortality
- Infection by encapsulated organisms is most common at all ages
- Functional asplenia:
    - As early as 6 months
    - By age 5 in most children

Board Pearl:
Fever in a child with sickle cell disease is a medical emergency.

Sickle Cell Anemia — Laboratory

- Anemia
- Sickle cells on smear

- Target cells
- Positive sickle prep
- Metabisulfite screen:
    - Positive in both disease and trait

Hemoglobin electrophoresis

- Disease:
    - 90% HbS
    - 8% HbF
    - 2% HbA_2
    - **No HbA**
- Trait:
    - 55% HbA
    - 43% HbS
    - 2% HbA_2

Board Pearl:
Absence of HbA confirms sickle cell disease.

Complication	Presentation	Diagnosis	Treatment
Fever	Fever is a medical emergency in patients with sickle cell disease.	CBC with differential, blood cultures, chest X-ray (if respiratory symptoms), urinalysis/urine culture when indicated.	**Hospital admission**, prompt empiric **IV third-generation cephalosporin** (e.g., ceftriaxone or cefotaxime). Continue **penicillin prophylaxis** through 5 years of age (longer in selected high-risk patients).

Dactylitis (Hand-Foot Syndrome)	Painful inflammation and swelling of the hands and feet; often the **first manifestation** of sickle cell disease in infancy; usually bilateral.	Clinical diagnosis based on characteristic painful swelling of the hands and/or feet.	Analgesics, hydration, and supportive care.
Vaso-occlusive crisis (Pain crisis)	Acute pain involving the extremities, chest, abdomen, back, or joints due to vaso-occlusion.	Clinical diagnosis; evaluate for complications and exclude alternative causes of pain.	Adequate analgesia, hydration, incentive spirometry (when indicated), and disease modification with **hydroxyurea** for recurrent crises.
Renal disease	Gross hematuria, impaired urine-concentrating ability (hyposthenuria), pyelonephritis, proteinuria.	Urinalysis, urine albumin/protein assessment, renal function tests; evaluate for papillary necrosis when suspected.	Nephrology referral; treat the underlying renal complication and optimize sickle cell disease management.

Complication	Presentation	Diagnosis	Treatment
Acute Chest Syndrome	Fever, chest pain, cough, hypoxemia, respiratory distress	Chest X-ray (new pulmonary infiltrate), pulse oximetry, CBC, blood cultures	Oxygen, analgesia, IV fluids (avoid overhydration), incentive spirometry, empiric antibiotics (e.g., ceftriaxone + azithromycin), simple or exchange transfusion if severe

Stroke	Sudden headache, focal neurologic deficits, weakness, seizures, altered mental status	Brain MRI/MRA (or emergent CT if hemorrhage suspected); Transcranial Doppler (TCD) for screening	Urgent exchange transfusion (preferred) or simple transfusion if exchange is unavailable; chronic transfusion therapy for secondary prevention. Children with abnormal TCD ≥200 cm/sec should receive chronic transfusions to maintain HbS <30%
Aplastic Crisis (Parvovirus B19)	Pallor, fatigue, weakness, decreased activity, poor feeding; sudden worsening of anemia	Marked drop in hemoglobin with reticulocytopenia; Parvovirus B19 PCR or IgM if needed	Supportive care; packed RBC transfusion if symptomatic or severe anemia
Splenic Sequestration Crisis	**Rapidly enlarging spleen, pallor, tachycardia, weakness, hypovolemic shock**	**Acute drop in hemoglobin with reticulocytosis and thrombocytopenia; clinical diagnosis ± abdominal ultrasound**	**IV fluids, urgent packed RBC transfusion; consider splenectomy for recurrent episodes**
Priapism	**Painful prolonged penile erection lasting >4 hours**	**Clinical diagnosis; penile Doppler ultrasound if diagnosis is uncertain**	**Hydration, analgesia, urology consultation; corporal aspiration and irrigation with intracavernosal phenylephrine if persistent (>4 hours); exchange transfusion is not first-line but may be considered in selected refractory cases**

Methemoglobinemia

Definition

Methemoglobinemia is caused by oxidation of hemoglobin iron from the ferrous (Fe^{2+}) state to the ferric (Fe^{3+}) state, resulting in impaired oxygen delivery to tissues.

Etiology

Congenital

- Cytochrome b5 reductase deficiency
- Hemoglobin M disease

Acquired (more common)

- Benzocaine or other topical anesthetics
- Dapsone
- Nitrates/nitrites (including contaminated well water)
- Nitric oxide
- Aniline dyes
- Severe gastroenteritis (especially infants)

Clinical Features

- Cyanosis despite oxygen therapy
- Chocolate-brown (dark brown) blood
- Blood remains brown after exposure to 100% oxygen
- Headache
- Fatigue
- Dyspnea
- Confusion
- Seizures and coma in severe cases

Severity

- 10–15%: Visible cyanosis
- 20–30%: Symptoms begin
- >50%: Severe neurologic and cardiovascular symptoms
- >70%: Often fatal

Diagnosis

- Pulse oximetry usually around 85%
- Normal PaO_2 on arterial blood gas
- Confirm with co-oximetry

Treatment

- Remove offending agent
- Oxygen
- Methylene blue (1–2 mg/kg IV) for symptomatic patients or significant methemoglobinemia
- Avoid methylene blue in G6PD deficiency
- Vitamin C may be considered when methylene blue is contraindicated

Board Pearl

- **Chocolate-brown blood that does not turn red with oxygen exposure is classic for methemoglobinemia.**
- **Normal PaO_2 with low oxygen saturation strongly suggests the diagnosis.**
- **Do not administer methylene blue to patients with G6PD deficiency because it may worsen hemolysis.**

Pyruvate Kinase Deficiency

Etiology

- Autosomal recessive disorder
- One of the most common RBC enzyme deficiencies
- ATP depletion causes premature destruction of RBCs

Pathophysiology

Pyruvate kinase catalyzes the final step of glycolysis, producing ATP.

ATP deficiency results in:

- Membrane rigidity
- Extravascular hemolysis
- Chronic hemolytic anemia

Clinical Features

- Neonatal jaundice
- Pallor
- Jaundice
- Splenomegaly
- Pigment gallstones
- Iron overload may develop even without frequent transfusions

Laboratory Findings

- Normocytic hemolytic anemia
- Reticulocytosis
- Elevated indirect bilirubin
- Elevated LDH
- Low haptoglobin

Diagnosis

- Reduced pyruvate kinase enzyme activity
- Molecular genetic testing confirms diagnosis

Treatment

- Folic acid supplementation
- Transfusion when necessary
- Splenectomy in selected severe patients

- Iron chelation if transfusion-related iron overload develops

Board Pearl

- Pyruvate kinase deficiency causes ATP depletion—not oxidative damage.
- Chronic extravascular hemolysis distinguishes it from G6PD deficiency**.**

Glucose-6-Phosphate Dehydrogenase (G6PD) Deficiency

Etiology

- X-linked recessive
- Common in African, Mediterranean, Middle Eastern, and Asian populations

Pathophysiology

G6PD generates NADPH, which maintains reduced glutathione.

Without adequate G6PD:

- RBCs cannot neutralize oxidative stress.
- Hemoglobin denatures forming Heinz bodies.
- Splenic macrophages remove Heinz bodies producing bite cells.

Common Triggers

Drugs

- Sulfonamides
- Dapsone
- Primaquine
- Nitrofurantoin
- Rasburicase

Other

- **Fava beans**
- **Acute infections**
- **Neonatal period**

Clinical Features

- Sudden pallor
- Jaundice
- Dark urine
- Fatigue
- Neonatal hyperbilirubinemia

Laboratory Findings

- Normocytic hemolytic anemia
- Reticulocytosis
- Elevated indirect bilirubin
- Elevated LDH
- Low haptoglobin
- Heinz bodies (supravital stain)
- Bite cells (peripheral smear)

Diagnosis

Reduced G6PD enzyme activity.

Testing should be repeated several weeks to months after recovery because young RBCs may produce a false-normal result during acute hemolysis.

Treatment

- Avoid oxidative triggers
- Treat infections promptly
- Supportive care
- Blood transfusion for severe anemia (rare)
- Folic acid supplementation for chronic hemolysis

Board Pearl

- **Heinz bodies require supravital stain; bite cells are seen on routine peripheral smear.**
- **Do not measure G6PD activity during an acute hemolytic episode because results may be falsely normal.**
- **Hemolysis is usually self-limited because the oldest RBCs are destroyed first.**

Autoimmune Hemolytic Anemia (AIHA)

Etiology

Autoantibodies directed against RBC surface antigens.

Warm AIHA

- IgG-mediated
- Most common type in children

Cold AIHA

- IgM-mediated
- Often follows Mycoplasma pneumoniae or Epstein-Barr virus infection

Clinical Features

- Pallor
- Fatigue
- Jaundice
- Dark urine
- Splenomegaly
- Fever

Laboratory Findings

- Severe anemia
- Reticulocytosis
- Elevated indirect bilirubin
- Elevated LDH
- Low haptoglobin
- Positive direct antiglobulin (Coombs) test
- Spherocytes
- Elevated MCHC

Diagnosis

Positive Direct Antiglobulin (Direct Coombs) Test

Treatment

Mild disease

- Observation and supportive care

Moderate to severe disease

- Corticosteroids (first-line)
- Blood transfusion if clinically indicated
- IVIG in selected patients
- Rituximab for steroid-refractory disease
- Splenectomy rarely required

Board Pearl

- **Positive Direct Coombs test is the hallmark of AIHA.**
- **Warm AIHA = IgG; Cold AIHA = IgM.**
- **Spherocytes with a positive Coombs test strongly suggest warm AIHA.**
- **Rituximab has largely replaced splenectomy as second-line therapy in many children.**

Neutropenia

Absolute Neutrophil Count (ANC)

- Mild:
    - ANC **1000–1500**
- Moderate:
    - ANC **500–1000**
- Severe:
    - ANC **<500**
- Risk of infection:
    - Duration and severity correlate with infection risk
    - ANC persistently <100/μL for >3–4 weeks → infection risk approaches **100%**

Neutropenia — Examples

- ANC <500/μL due to viral infection:
    - Transient
    - Not life-threatening
    - No antibiotic prophylaxis unless febrile
- ANC <500/μL in febrile child on chemotherapy:
    - Life-threatening
    - Requires immediate evaluation
    - Blood cultures + empiric broad-spectrum antibiotics
- ANC <100/μL due to severe congenital neutropenia (Kostmann syndrome):
    - Most dangerous
    - Most life-threatening

Board Pearl:
Febrile neutropenia in oncology patients is a medical emergency.

Neutropenia

Causes

- Acute viral infection:
    - Epstein-Barr virus
    - RSV
    - HHV-6
- Bacterial infection
- Hypersplenism
- Drug-induced:
    - Sulfonamides

    - Penicillin
    - Ibuprofen

Cyclic Neutropenia (Chronic)

- Autosomal dominant
- Mutation in **ELANE** gene

Clinical Presentation

- Neutropenia every **21 days**
- Lasts **3–6 days**
- Severe neutropenia during nadir:
    - Fever
    - Oral ulceration
    - Gingivitis
    - Pharyngitis
    - Skin infections

Cyclic Neutropenia

Laboratory

- CBC **2–3 times/week for 6 weeks**

Treatment

- Prophylactic G-CSF during nadir (selected cases)
- Immediate attention with fevers

Board Pearl:
Periodic neutropenia every 21 days is diagnostic of cyclic neutropenia.

Chronic Benign Neutropenia

- Typically presents <3 years of age
- No serious infections
- Diagnosis of exclusion
- No treatment necessary except attention with fevers

Autoimmune Neutropenia

- More severe
- ANC may drop to zero
- Positive antineutrophil antibodies

Management

- Treat inter-current infections
- Prophylactic Bactrim if frequent infections
- G-CSF decreases infection frequency
- Spontaneous recovery in **6–24 months** is typical

Board Pearl:
Autoimmune neutropenia in young children is usually self-limited.

Kostmann Syndrome (Severe Congenital Neutropenia)

- Autosomal recessive
- Mutation in **ELANE** gene
- Very rare and very aggressive

Clinical Presentation

- Mouth ulcers
- Gingivitis
- Otitis media
- Cellulitis

- Respiratory infections

Kostmann Syndrome

Clinical Presentation (continued)

- Skin infections and abscesses (most common)
- Pneumonia and deep tissue abscesses (life-threatening)
- Mild hepatosplenomegaly

Complications

- Progression to MDS / AML

Treatment

- G-CSF
- Stem cell transplant for MDS/AML

Board Pearl:
Severe congenital neutropenia carries high leukemia risk.

IMPORTANT

- **Never take rectal temperature** in a neutropenic or oncologic patient

Board Pearl:
Rectal exams increase the risk of bacteremia in neutropenic patients

Congenital Amegakaryocytic Thrombocytopenia

- Diagnosis
    - Initially absent megakaryocytes
    - Then pancytopenia
    - If beyond neonatal periods:
        - Bone marrow aspirate and biopsy will confirm the diagnosis

Board Pearl:
Absent megakaryocytes with progression to pancytopenia is classic for congenital amegakaryocytic thrombocytopenia.

Thrombocytopenia Absent Radius Syndrome (TARS)

- Rare autosomal recessive disease

Clinical Presentation

- Thrombocytopenia
- Absent radius
- Congenital heart disease:
    - TOF
    - ASD
    - VSD
- Other:
    - Eosinophilia
    - Milk protein allergy
    - Leukemoid reaction
    - Intellectual disability

Outcome

- Platelet number improve in the first year
- Transfusion support for bleeding

Board Pearl:
TARS = thrombocytopenia with **present thumbs** and absent radius.

High Yield – Thrombocytopenia

- Platelet destruction

Immune

- ITP
- Drugs

Non-Immune

- TTP
- HUS
- DIC
- Infection
- Cardiac

Immune Thrombocytopenia (ITP)

Etiology

- Antiplatelet antibody
- Often a few weeks after infection

Clinical Presentation

- Usually healthy appearing child
- Petechiae
- Ecchymoses
- Epistaxis

Immune Thrombocytopenia (ITP)

Major Risk

- Intracranial hemorrhage

Laboratory

- CBC with peripheral smear
- Thrombocytopenia
- Normal RBCs and WBCs

- Normal to increased size of platelets (MPV)
- No excess red cell fragments (no TTP)

Board Pearl:
Large platelets with isolated thrombocytopenia suggest ITP.
In ITP, management is based on bleeding severity, not platelet number alone.

Immune Thrombocytopenia (ITP)

Treatment

- Observation (mild bleeding)
- No contact sports → prevent head trauma
- No NSAIDs
- Resolve 85% in 6 months

Moderate to Severe Bleeding

- **First-line**
    - Corticosteroids
    - IVIG
- Immunosuppressants (e.g., Rituximab)
- Thrombopoietin receptor agonists (Eltrombopag)
- Splenectomy
- Platelet transfusion reserved for life-threatening conditions
- Close observation regardless of platelet count even if <10,000

Board Pearl:
Platelet transfusion is avoided in ITP unless bleeding is life-threatening.

Hemolytic Uremic Syndrome (HUS)

Background

- Non-immune
- E. coli O157:H7 most common
- Shigella dysenteriae type I
- Endothelial injury to small blood vessels →
    - Clot formation
    - Acute kidney injury
    - Hemolysis
    - Low platelets

Clinical Presentation

- Children 4 months–2 years
- GI symptoms:
    - Vomiting
    - Often bloody diarrhea
- Oliguria
- Hypertension

Triad

- Destruction of RBCs
- Low platelets
- Acute kidney injury

Hemolytic Uremic Syndrome

Laboratory

- Thrombocytopenia
- Anemia (can be severe)
- Peripheral smear:
    - Schistocytes

    - Spherocytes
- Elevated BUN and creatinine
- Urinalysis:
    - Mild proteinuria
    - RBCs
    - RBC casts
- Stool culture

Treatment

- Maintain fluids and electrolytes
- Blood pressure control
- Aggressive management of renal failure
- Correction of anemia with transfusion
- Avoid antibiotics in most cases

Board Pearl:
Antibiotics can worsen toxin-mediated HUS.
Bloody diarrhea followed by anemia, thrombocytopenia, and AKI = HUS.

Thrombotic Thrombocytopenic Purpura (TTP)

Etiology

- Congenital or acquired
- ADAMTS13 gene absence or autoantibodies
- Large vWF multimers →
    - Microangiopathy
    - Clot formation

Clinical Presentation (Pentad)

- Microangiopathic hemolytic anemia
- Thrombocytopenic purpura

- Neurologic abnormalities
- Fever
- Renal disease

Thrombotic Thrombocytopenic Purpura (TTP)

Laboratory

- Thrombocytopenia
- Blood smear:
    - Schistocytes
    - Microspherocytes
    - Nucleated RBCs
- Elevated vWF antigen
- Severe deficiency of ADAMTS13 activity
- Reduced haptoglobin
- Hemoglobinuria
- Hemosiderinuria

Management

- Plasmapheresis
- Rituximab
- Vincristine
- Cyclophosphamide
- **Platelet transfusion can worsen neurologic symptoms**

Board Pearl:
Plasmapheresis is lifesaving in TTP.

Wiskott–Aldrich Syndrome (WAS)

- X-linked
- Occurs only in males

Clinical Presentation

- Petechiae
- Spontaneous nose bleeds
- Bloody diarrhea
- Thrombocytopenia
- **Small-sized platelets**
- Eczema
- Recurrent infections
    - Low IgM
    - Elevated IgA and IgE
- SCT is curative

Board Pearl:
Small platelets differentiate WAS from ITP.

Bernard–Soulier Syndrome

- Autosomal recessive
- Severe platelet dysfunction
- Thrombocytopenia
- **Giant platelets**
- Markedly prolonged bleeding time
- Defect in **GPIb/IX/V**
- vWF interaction impaired

Glanzmann Thrombasthenia

- Autosomal recessive
- Defect in **GPIIb/IIIa**
- Severe platelet dysfunction
- Prolonged bleeding time
- Normal platelet count
- Abnormal aggregation studies

Treatment

- Platelet transfusion

Kasabach–Merritt Syndrome

- Vascular tumor
- Thrombocytopenia
- Hemolytic anemia
- Coagulopathy
- Do not regress spontaneously
- Very aggressive
- Can be fatal

Coagulation Disorders

Mixing Study

- Prolonged PT or PTT
- Mix patient plasma with normal FFP 1:1
- If corrects → factor deficiency
    - Prolonged PT → factor VII
    - Prolonged PTT → factors VIII, IX, XI, XII
- If does not correct → inhibitor

    - Lupus anticoagulant
    - Antiphospholipid syndrome

Hemophilia

- X-linked recessive
- Factor VIII (Hemophilia A) – 85%
- Factor IX (Hemophilia B) – 10–15%

Severity

- Severe: <1%
- Moderate: 1–5%
- Mild: >5%

Clinical Presentation

- Easy bruising
- Intramuscular hematomas
- Hemarthroses (hallmark)

Von Willebrand Disease (VWD)

Keywords

- Recurrent mucocutaneous bleeding
- Family history
- Study of choice:
    - vWF activity assay

Types

- Type 1: Autosomal dominant (75%)
- Type 2: Qualitative defects
- Type 3: Autosomal recessive, severe

Treatment

- DDAVP for type 1
- vWF/FVIII concentrates for type 2B and 3

DIC

Pathophysiology

- Widespread clotting activation
- Consumption of platelets and factors

Laboratory

- Prolonged PT and PTT
- Low fibrinogen
- Low platelets
- Elevated D-dimer

Treatment

- Treat underlying cause
- Replace components as needed

Transfusion

PRBCs

- Dose: 10–20 mL/kg
- WBC filtered
- Irradiated for immunocompromised

FFP Indications

- Volume replacement
- Coagulation factor deficiency

Reference:

Ajebade, O., Blankenhorn, K., King, Z., Morrone, K. (2024). Hematology/Oncology. In: Naga, O. (eds) Pediatric Board Study Guide. Springer, Cham. https://doi.org/10.1007/978-3-031-65148-9_10