NOTES
NORMOCYTIC ANEMIA (INCREASED HEMOLYSIS)

GENERALLY, WHAT IS IT?

PATHOLOGY & CAUSES

- Inherited/acquired disorders resulting in premature destruction of normal red blood cells (RBCs)

SIGNS & SYMPTOMS

- If hematopoietic compensation insufficient, anemic symptoms (e.g. pallor, fatigue, activity intolerance)
- Intravascular hemolysis → hemoglobinuria, iron deficiency
- Extravascular hemolysis → jaundice, splenomegaly, gallstone formation

DIAGNOSIS

LAB RESULTS

- Complete blood count (CBC)
- Peripheral blood smear analysis
- Measure plasma for hemolysis indicators
  - Bilirubin, lactate dehydrogenase (LDH), haptoglobin
- Measure specific indicators of hemolysis in urine
  - Hemoglobin, bilirubin, hemosiderin

TREATMENT

- See individual disorders

AUTOIMMUNE HEMOLYTIC ANEMIA (AHA)

osms.it/autoimmune-hemolytic-anemia

PATHOLOGY & CAUSES

- Anemia caused by immune destruction of red blood cells by autoantibodies against antigens on RBCs surface
- AKA AIHA

TYPES

Warm AIHA

- Most common
- "Warm" because optimum temperature for antibody to react with RBCs = normal body temperature (37°C/98.6°F)
- *Predominant autoantibody:* IgG (IgA and IgM may also be involved)
- *Predominant RBC antigen:* Rh
- Associated with immune deficiencies, malignancies, certain drugs
- Antibody fixes complement + binds to RBC membrane → antibody-coated RBCS destroyed in spleen
  - *Usual site of hemolysis:* extravascular, by macrophages in spleen, liver

Cold AIHA

- "Cold" because optimum temperature for antibody to react with RBCs = below normal body temperature (4°C/39.2°F)
- *Predominant autoantibody:* IgM
- *Predominant RBC antigen:* I, i, P
- Antibodies activate direct complement system attack
- *Usual site of hemolysis:* intravascular, complement-mediated
- Paroxysmal cold hemoglobinuria
  - Most common in children
  - Caused by Donath–Landsteiner antibody
  - Associated with viral (e.g. measles, varicella) or bacterial (e.g. mycoplasma, *H. influenza*) infections
- Cold agglutinin syndrome
  - Most common in adults > 70 years old
  - Primarily biologically-female individuals
  - Associated with lymphoproliferative disorders, autoimmune disorders, mycoplasma infections

AUTOIMMUNE HEMOLYTIC ANEMIA CLASSIFICATIONS

WARM	COLD
PRIMARY: Idiopathic	ACUTE: Infections
SECONDARY: Chronic autoimmune disease, B-cell neoplasms, infections, medications	CHRONIC: Idiopathic; B-cell neoplasms

RISK FACTORS

- Exposure to cold
- Administration of offending drug
- Development of associated diagnosis
  - Infection, malignancy, autoimmune disorder

COMPLICATIONS

- Depend on type/degree of hemolysis
- Anemia, venous thromboembolism, cholelithiasis, renal insufficiency
- *Older individuals:* increased risk of cardiac complications

SIGNS & SYMPTOMS

- Onset insidious/acute
- If hematopoietic compensation insufficient, anemic signs and symptoms (e.g. pallor, fatigue, activity intolerance)
- If severe anemia/underlying cardiac disease, a hyperdynamic state (e.g. bounding pulses, tachycardia, pulmonary congestion)
- Cold AIHA
  - Hemoglobinuria after exposure to cold temperatures
- Paroxysmal cold hemoglobinuria
  - Jaundice, hemoglobinuria, anemia after infection; pain in legs, back following exposure to cold
- Cold agglutinin syndrome
  - Anemia, acrocyanosis, or Raynaud's phenomenon

DIAGNOSIS

LAB RESULTS

- Evidence of hemolysis
  - Increased lactate dehydrogenase (LDH)
  - Increased indirect bilirubin
  - Decreased haptoglobin
- Increased mean corpuscular volume (MCV)
- Low hemoglobin, hematocrit
- Reticulocytosis
- Direct antibody (DAT)
  - *Warm:* positive for IgG/IgG + C3d
  - *Cold:* positive for C3d
- Partial macrophage phagocytosis → spherocytosis

TREATMENT

- *Cold AIHA:* often no treatment required

MEDICATIONS

- Corticosteroids
- *Monoclonal antibody:* rituximab
- Immunosuppressants

SURGERY

- Splenectomy (reduces hemolysis)

OTHER INTERVENTIONS

- Eliminate triggers (e.g. cold, drugs)
- Correct anemia
  - Folic acid supplements to support erythropoiesis
  - Blood transfusion

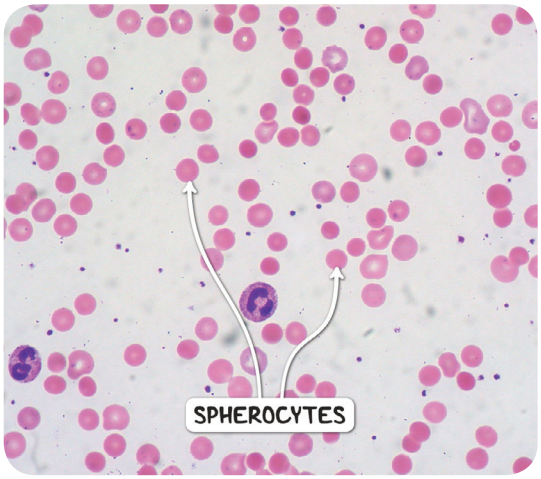

Figure 54.1 A peripheral blood smear from an individual with warm autoimmune hemolytic anemia. There are numerous spherocytes present due to degradation of the red cell membrane by macrophages.

GLUCOSE-6-PHOSPHATE DEHYDROGENASE DEFICIENCY

osms.it/G6PD

PATHOLOGY & CAUSES

- Hematological enzymopathy where deficient glucose-6-phosphate dehydrogenase (G6PD) causes premature hemolysis
- Inherited, X-linked mutation of *G6PD* gene
- Hemolysis can be acute/intermittent/chronic (rare)
- Inadequate G6PD, GSH → oxidative stress → build-up of free radicals, peroxides → precipitation of hemoglobin → disruption of cell membrane → increased cellular rigidity → extravascular hemolysis, accelerated removal of damaged RBCs by reticuloendothelial system in spleen; intravascular hemolysis may also occur
- Hemolysis precipitated by sources of oxidative damage that trigger hemolysis.
  - RBCs with deficient G6PD have a decreased lifespan
  - Certain drugs (sulfa drugs, antimalarials) and chemicals (e.g. henna compounds, aniline-based dyes, naphthalene) interact with hemoglobin + oxygen → hydrogen peroxide (H_2O_2), other oxidizing radicals within cell → hemoglobin precipitation
- Infections → possible generation of hydrogen peroxide by leukocytes/exposure to neutrophil produced oxidants → hemoglobin precipitation
- Ingestion of fava beans (favism)

W.H.O. Classifications

- Based on degree of enzyme deficiency, resulting hemolysis
- *Class I:* G6PD < 10% of normal; chronic hemolytic anemia
- *Class II:* G6PD < 10% of normal; intermittent hemolysis when exposed to

oxidative stress
    - *G6PD Mediterranean:* majority of RBCs hemolyze in setting of oxidative stress; half-life of G6PD especially short (measured in hours)
- *Class III:* G6PD 10–60% of normal; intermittent hemolysis when exposed to trigger
    - *G6PD A- :* only oldest RBCs hemolyze in setting of oxidative stress; G6PD half-life = 13 days (normal = 62 days)

TYPES
- Acute hemolysis
    - May be mild/severe (life-threatening)
- Kernicterus
    - G6PD-related neonatal jaundice → kernicterus if not promptly treated
- Renal failure

RISK FACTORS
- Most common in people of African, Asian, Mediterranean descent

SIGNS & SYMPTOMS
- Generally asymptomatic until exposed to oxidative stress
- Acute hemolysis
    - Pallor, jaundice, dark urine
    - Abdominal/back pain due to increased splenic activity
    - Renal insufficiency (severe hemolysis)
- Favism (potentially fatal acute hemolysis)

DIAGNOSIS
LAB RESULTS
- Decreased hemoglobin
- Heinz bodies
    - Caused by precipitation of oxidized, denatured hemoglobin
- Bite cells
    - Cells have bitten appearance where macrophages have removed bits of precipitated hemoglobin from RBC
- Blood chemistry demonstrates evidence of hemolysis
    - Elevated indirect bilirubin
    - Elevated lactate dehydrogenase (LDH)
    - Decreased haptoglobin
- Reticulocytosis
- Hemoglobinuria, hemosiderinuria
- G6PD assay
    - Directly measures G6PD activity in RBCs; false-negative if testing done during/immediately after acute hemolytic episode
- Screening tests
    - *Fluorescent spot test:* glucose-6-phosphate + NADP added to hemolysate of individual's RBCs → fluorescence of NADPH
    - *Methemoglobin reduction test:* methylene blue measures transfer of hydrogen ions from NADPH to methemoglobin → indirectly estimates NADPH generation
    - *Newborn screening:* blood analyzed for biochemical, genetic markers of G6PD, other inherited disorders
- Confirmatory test to assay NADPH formation performed after positive screening test/as initial test
    - Spectrophotometric analysis of RBC hemolysate + glucose-6-phosphate + NADP measures NADPH generation rate

TREATMENT
MEDICATIONS
- Folic acid supplements (support erythropoiesis)

OTHER INTERVENTIONS
- Eliminate triggers
- Manage acute hemolytic episodes
    - Hydration
    - Transfusions
- Phototherapy, exchange transfusion
    - Neonatal jaundice

HEMOLYTIC DISEASE OF THE NEWBORN

osms.it/hemolytic-disease-of-the-newborn

PATHOLOGY & CAUSES

- Anemia caused by hemolytic destruction of fetal/neonatal erythrocytes by maternal antibodies
- AKA alloimmune HDFN/erythroblastosis fetalis

CAUSES

- Fetomaternal hemorrhage exposes maternal circulation to antigens present on fetal RBCs → maternal sensitization → formation of maternal IgG antibodies against fetal RBCs → IgG antibodies small enough to cross placenta → antibody attachment to fetal cells → agglutination (clumping) → microcirculatory impairment → hemolysis, destruction of RBCs by macrophages in reticuloendothelial system
  - Involves Rhesus (Rh) blood group/A, B, AB, O blood groups
- Causes of maternal sensitization include normal delivery, spontaneous/induced abortion, chorionic villus sampling, amniocentesis, antenatal hemorrhage, maternal trauma, idiopathic
  - Small amount (0.1mL) of fetal blood needed to induce maternal immune response
- Rh incompatibility
  - Rh negative mother exposed to Rh positive fetal RBCs → maternal anti-D antibodies formed
  - Usually will not affect first pregnancy when initial exposure occurs; adversely affects subsequent pregnancies
  - Decreasing occurrence due to availability of Rh(D) immune globulin prophylaxis
- ABO incompatibility
  - More common, less severe morbidity, mortality than with Rh incompatibility
  - Occurs in type O mother with naturally-occurring Anti-A and Anti-B antibodies + Type A/Type B fetus
  - Can occur in first and all subsequent pregnancies

RISK FACTORS

- Blood group incompatibility, fetomaternal hemorrhage

COMPLICATIONS

- Anemia, hyperbilirubinemia, kernicterus
- Growth restriction, hydrops fetalis, erythroblastosis fetalis
  - Increased immature RBCs in fetal circulation

SIGNS & SYMPTOMS

- Hemolytic disease caused by ABO incompatibility
  - Mild to moderate hyperbilirubinemia within first 24h of life
  - Mild to moderate anemia
- Hemolytic disease caused by Rh incompatibility (more severe)
  - *Hyperbilirubinemia, kernicterus:* possible
  - *Symptomatic anemia:* pallor, lethargy, tachycardia, tachypnea
  - *Hydrops fetalis:* related to severe anemia-induced hypoxia; subcutaneous edema, pleural/pericardial effusion, ascites, signs and symptoms of shock
- Antenatal presentation
  - Intrauterine growth restriction signals problems with ongoing hemolysis, hypoxia

DIAGNOSIS

DIAGNOSTIC IMAGING

Doppler ultrasound

- Antenatal (maternal testing)
- Notes growth restriction/presence of hydrops

LAB RESULTS

- Antenatal (maternal testing)
  - *Positive indirect antiglobulin test:* IAT, indirect Coombs test; demonstrates IgG antibodies in maternal serum
  - *Kleihauer–Betke test:* positive if fetomaternal hemorrhage has occurred
  - *Percutaneous umbilical blood sampling (PUBS):* measures hemoglobin, hematocrit, identifies fetal blood type
  - *Spectrophotometric amniotic fluid analysis:* increased bilirubin if significant hemolysis has occurred
- Postnatal (neonatal testing)
  - *Blood typing:* confirm incompatibility of maternal, neonatal blood types
  - *Positive direct antiglobulin test:* DAT, direct Coombs test; evidence of maternal antibodies on RBC surface
  - *Positive indirect antiglobulin test:* IAT, indirect Coombs test; evidence of maternal antibodies in serum
  - *Transcutaneous bilirubin (TcB), serum bilirubin:* increased
  - *CBC:* decreased RBCs, reticulocytosis, decreased hemoglobin and hematocrit
  - *Peripheral blood smear analysis:* evidence of hemolysis; polychromasia, microspherocytosis (seen in ABO incompatibility)

TREATMENT

MEDICATIONS

- Hematopoietic agents (epoetin alfa/darbepoetin), iron supplements
  - Anemia

OTHER INTERVENTIONS

- RBC transfusion
  - Anemia, hydrops fetalis
- Exchange transfusion
  - Hyperbilirubinemia, hydrops fetalis
- Phototherapy
  - Hyperbilirubinemia
- Intravenous immunoglobulin (IVIG)
  - Hyperbilirubinemia
  - Reduces hemolysis, bilirubin production
- Pericardiocentesis, paracentesis, thoracentesis
  - Hydrops fetalis; as indicated for pericardial effusion, pleural effusion, ascites
- Intrauterine RBCl transfusion
  - Hydrops fetalis if diagnosed antenatally

HEREDITARY SPHEROCYTOSIS

osms.it/hereditary-spherocytosis

PATHOLOGY & CAUSES

- Inherited RBC membrane defect causing destabilization of cellular membrane, resulting in chronic, premature extravascular hemolysis
- Autosomal dominant (75%) or autosomal recessive (25%)
- Mutations of genes encoding for proteins that secure RBC membrane skeleton to plasma membrane → membrane destabilization → rigidity, resistance to deformability → hemolysis

TYPES

Mild (20–30%)

- Mild anemia, splenomegaly, jaundice; modest reticulocytosis; normal hemoglobin
- Adolescents/adults most commonly diagnosed

Moderate (60–70%)

- Moderate anemia, reticulocytosis, hyperbilirubinemia
- Require occasional transfusions
- Infants/children most commonly diagnosed

Severe (5%)

- Marked anemia, hyperbilirubinemia, splenomegaly
- Regular transfusions needed

RISK FACTORS

- Most common in people of Northern European descent

COMPLICATIONS

- Transient aplastic crisis caused by infections (e.g. parvovirus B19)
- Megaloblastic anemia related to folate deficiency
- Neonatal icterus; non-immune hydrops fetalis with fetal death if disease = severe

SIGNS & SYMPTOMS

- Jaundice
- Anemic signs and symptoms (e.g. pallor, fatigue, activity intolerance)
- Splenomegaly

DIAGNOSIS

LAB RESULTS

- Decreased hemoglobin
- Reticulocytosis
- Spherocytosis
  - Morphology = sphere-shaped (normal = biconcave)
- Presence of schistocytes (RBC fragments)
- Slightly decreased to normal MCV
  - *Spherocytes:* decreased MCV
  - *Reticulocytes:* increased MCV
- Elevated mean cell hemoglobin concentration (MCHC)
  - Secondary to dehydration, loss of cellular membrane
- Elevated red cell distribution width (RDW)
- Evidence of hemolysis
  - Elevated indirect bilirubin
  - Elevated lactate dehydrogenase (LDH)
  - Decreased haptoglobin
- Osmotic fragility test, acidified glycerol lysis test (AGLT)
  - Identifies spherocytes which lyse in hypotonic solutions at higher rate than normal RBCs
- Cryohemolysis test
  - Uses hypertonic solution, temperature manipulation to identify spherocytes which lyse at higher rate than normal RBCs
- Eosin-5-maleimide (EMA) binding test
  - Flow cytometric test to observe cell membrane protein interaction with eosin-5-maleimide dye

- Osmotic gradient ektacytometry
  - Measures surface area to volume, cell hydration, membrane deformability

TREATMENT

SURGERY

- Splenectomy

OTHER INTERVENTIONS

- Blood transfusions
- Phototherapy, exchange transfusions
  - Neonatal hyperbilirubinemia
- Folic acid supplements
  - Support hematopoiesis

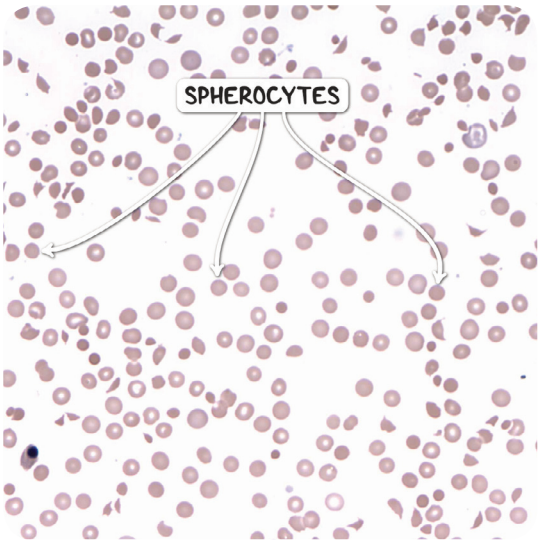

Figure 54.2 A peripheral blood smear demonstrating sphere shaped erythrocytes in an individual with hereditary spherocytosis. The erythrocytes have lost their biconcave shape.

PAROXYSMAL NOCTURNAL HEMOGLOBINURIA (PNH)

osms.it/paroxysmal-nocturnal-hemoglobinuria

PATHOLOGY & CAUSES

- Inherited, X-linked hematologic stem cell disorder resulting in nocturnal hemolysis, hemolytic anemia, bone marrow failure, thrombosis

CAUSES

- Mutation of *PIGA* gene in hematopoietic stem cells
  - *PIGA* required for synthesis of glycosylphosphatidylinositol (GPI) protein on cell surface
  - GPI anchors glycoproteins on erythrocyte surface, protecting cell from lysis by attenuating activity of complement
- GPI protein absence or deficiency → ↑ susceptibility to complement activity → complement-mediated intravascular hemolysis
- Three phenotypes of RBCs categorized according to amount of GPI-anchored proteins on cell surface
  - *Type I:* normal
  - *Type II:* decreased
  - *Type III:* absent

RISK FACTORS

- Hemolysis in PNH cases increases in setting of increased complement activation
  - Infections
  - Surgery
  - Blood transfusions
  - Strenuous exercise
  - Excessive alcohol use

COMPLICATIONS

- Intravascular, extravascular hemolysis → anemia
- Consequences of hemoglobin-mediated nitric oxide scavenging
  - Intravascular hemolysis → free hemoglobin → ↑ consumption of nitric oxide → smooth muscle dystonia, vasospasm (abdominal pain, esophageal spasm, erectile dysfunction)
- Venous, arterial thrombosis
  - Multifactorial etiology related to proinflammatory complement activity, decreased availability of nitric oxide with resulting vasoconstriction, endothelial cell activation, associated platelet aggregation/clot formation
  - Hepatic vein thrombosis (Budd–Chiari syndrome) → hepatomegaly, jaundice, ascites, gastric and/or esophageal varices
  - Intestinal vein thrombosis → ischemic colitis
  - Cerebral vein thrombosis → headache, neurologic effects
- Microvascular hemolysis + iron deposits in renal tubules → chronic kidney disease
- Bone-marrow failure, aplastic anemia related to hematopoietic stem cell injury
- Eculizumab treatments associated with Increased risk of life-threatening neisserial infections

SIGNS & SYMPTOMS

- Variable according to degree of GPI-anchored protein loss → hemolysis
- Intermittent episodes (paroxysms) of hemoglobinuria
  - Dark urine
  - Hemolysis during night
- Clinical manifestations of anemia; e.g. pallor, fatigue, exertional dyspnea

DIAGNOSIS

LAB RESULTS

- Range from normal to abnormal according to degree of GPI-anchored protein loss, resulting hemolysis
- RBCs normal morphologically (pancytopenia may be evident in setting of bone marrow failure)
- Occasional poikilocytosis, anisocytosis
- Normochromic
- Normal to extremely decreased serum hemoglobin
- Reticulocyte count ranges from normal to decreased
- Evidence of hemolysis
  - Elevated bilirubin
  - Decreased haptoglobin
  - Elevated LDH
- Direct antiglobulin (DAT/Coombs) positive
- Hemoglobinuria, hemosiderinuria

OTHER INTERVENTIONS

- Bone marrow examination may indicate hypocellularity
- Flow cytometry

TREATMENT

MEDICATIONS

- Eculizumab
  - Monoclonal antibody, reduces complement-mediated hemolysis
  - Vaccinate against Neisseria meningitidis
- Iron, folic acid supplements support erythropoiesis
- Therapeutic anticoagulation and/or thrombolysis, as indicated for thrombosis
- Immunosuppressive therapy if aplastic anemia present

SURGERY

- Allogeneic hematopoietic stem cell transplant

OTHER INTERVENTIONS

- Red blood cell transfusions as needed

PIRUVATE KINASE DEFICIENCY

osms.it/piruvate-kinase-deficiency

PATHOLOGY & CAUSES

- Hematological enzymopathy caused by deficient pyruvate kinase, resulting in chronic, premature hemolysis of RBCs, hyperactive erythropoiesis
- Inherited, autosomal recessive mutation of (PK-LR) pyruvate kinase-LR (liver-red cell) gene
  - Homozygous for single PK-LR mutation/ heterozygous for two mutations
- Hemolysis primarily extravascular (within spleen); intravascular hemolysis variable
- Pyruvate kinase
  - Tetramer enzyme, catalyzes transphosphorylation of phosphoenolpyruvate into pyruvate, ATP during glycolysis
  - Pyruvate kinase deficiency-related block in glycolysis → accumulation of 2,3-bisphosphoglycerate (2,3-BPG) → shifts oxyhemoglobin dissociation curve to right → improved oxygen delivery to tissues → better tolerance of hemolytic anemia

CAUSES

- Hemolytic mechanism is unclear; possibly
  - ATP deficiency
  - Apoptosis of erythroid progenitors in spleen (ineffective erythropoiesis)

RISK FACTORS

- Most common in white people of Northern European descent, Asian people of Chinese descent, genetically-isolated communities of Swiss/German descent

COMPLICATIONS

- Pigmented gallstone formation
- Iron overload-associated organ damage
- Megaloblastic anemia related to folate deficiency
- Accelerated hemolysis during pregnancy/ with oral contraceptive use
- Neonatal icterus/non-immune hydrops fetalis
- Transient aplastic crisis induced by infections (e.g. parvovirus B19)

SIGNS & SYMPTOMS

- Variable presentation ranging from compensated disease to transfusion-dependent anemia
- Anemic signs and symptoms
  - Pallor, shortness of breath, activity intolerance
- Jaundice, splenomegaly

DIAGNOSIS

LAB RESULTS

- Decreased RBC count, reticulocytosis
- Increased serum glycolytic 2,3-BPG
- Hemoglobinuria, hemosiderinuria
- Evidence of hemolytic anemia with one or both of
  - Low levels of erythrocytic PK enzymatic activity
  - PK-LR gene mutation
- Evidence of hemolysis
  - Elevated indirect bilirubin
  - Elevated lactate dehydrogenase (LDH)
  - Decreased haptoglobin

OTHER DIAGNOSTICS

- Clinical evidence of hemolysis
  - Jaundice, pigmented (bilirubin) gallstones

TREATMENT

SURGERY

- Splenectomy
  - Reduces hemolysis
- Allogeneic hematopoietic cell transplantation
  - May be curative

OTHER INTERVENTIONS

- RBC transfusions
  - Often chronic
- Chelation therapy
  - Reduces iron-related organ damage
- Folic acid supplementation
  - Supports erythropoiesis
- Phototherapy, exchange transfusion
  - Treats neonatal jaundice

SICKLE-CELL ANEMIA

osms.it/sickle-cell-anemia

PATHOLOGY & CAUSES

- Hemolytic anemia caused by sickle-cell disease (SCD)
- A group of inherited hemoglobinopathies caused by point mutation of beta globin gene → produces hemoglobin S (HbS)
- RBCs containing HbS tend to polymerize, deform into sickle/crescent-shaped forms when deoxygenated
  - *Triggers for deoxygenation:* cold, dehydration, insomnia, alcohol consumption, stressful situations, overexertion, hormonal changes
  - Deoxygenation may be idiopathic
- Sickled cells less deformable than normal RBCs
  - Decreased lifespan due to hemolysis

TYPES

HbSS

- Sickle-cell disease
  - Homozygous for HbS
  - Chronic hemolytic anemia

HbSC

- Milder form of sickle-cell disease
  - Heterozygous for HbS + abnormal hemoglobin C

HbSA

- Sickle-cell trait/benign carrier state
  - Heterozygous for HbS + hemoglobin A (normal hemoglobin)

HbS beta thalassemia

- Heterozygous for HbS + one beta thalassemia gene

HbSD, HbSE, HbSO

- Rare
- Heterozygous for HbS + one other abnormal hemoglobin (D, E, or O)

COMPLICATIONS

- Affect all body systems
- Hematologic
  - Anemia related to aplastic crisis involving temporary arrest of erythropoiesis
- Pain
  - Vaso-occlusion, tissue ischemia, infarction; dactylitis (acute pain in small bones of hands/feet especially in children)
- Increased risk of infection
  - Related to hyposplenism/asplenism, decreased tissue perfusion
- Central nervous system
  - Ischemic/hemorrhagic stroke; transient ischemic attack, seizures

- Cardiovascular
  - Myocardial infarction, dysrhythmias, cardiomyopathy, heart failure, venous thromboembolism, leg ulcers, sudden death
- Respiratory
  - Acute chest syndrome (fever, chest pain, hypoxemia, wheezing, cough, respiratory distress), pulmonary hypertension, disordered breathing during sleep with nocturnal hypoxemia
- Genitourinary, reproductive
  - Priapism, erectile dysfunction; pregnancy complications, fetal/neonatal or maternal (e.g. intrauterine growth restriction, fetal death, low birthweight; preeclampsia, thromboembolic events)
- Endocrine
  - Delayed growth, development
- Skeletal
  - Osteoporosis, bone infarction
- Sensory
  - Proliferative retinopathy, retinal detachment
- Systemic
  - Multiorgan failure related to ischemia and/or infarction

SIGNS & SYMPTOMS

- Mild to moderate anemia (e.g. fatigue, activity intolerance, extertional dyspnea)
- Hypersplenism
- Pain from acute vaso-occlusive crisis

DIAGNOSIS

- Findings variable depending on inheritance pattern, degree of hemolysis
- Pain indicates cell sickling, vaso-occlusion

LAB RESULTS

- Vaso-occlusion, hemolysis, splenic sequestration → decreased hemoglobin, hematocrit, RBC count
- Reticulocytosis
- Increased white blood cell (WBC) count
- Peripheral blood smear analysis
- Mostly normochromic, normocytic cells; polychromasia may be present secondary to reticulocytosis
- Sickled cells present in SCD but not sickle-cell trait
- Canoe-shaped (partially sickled) RBCs
- Howell Jolly bodies
  - Related to hyposplenia
- Normal-to-increased mean corpuscular volume (MCV)
- Target cells
- Diagnostic tests to determine organ damage (e.g. urinalysis → hematuria, albuminuria from renal papillary damage)
- Evidence of hemolysis
  - Elevated unconjugated bilirubin
  - Elevated lactate dehydrogenase (LDH)
  - Low haptoglobin
- Positive solubility test (Sickledex)
- Hemoglobin electrophoresis provides definitive diagnosis (90–95% HbS)

TREATMENT

- Prevent/reduce occurrence of crises (e.g. immunizations to prevent infection, manage stress, prevent deoxygenation)

MEDICATIONS

- Hydroxyurea
  - Increases cell deformability, decreases RBC endothelial adhesion, increases hemoglobin F levels; reduces sickling
- L-glutamine
  - Reduces sickling
- Pain management
  - Analgesics, adjunctive, non-pharmacological therapies

SURGERY

- Hematopoietic cell transplantation

OTHER INTERVENTIONS

- Blood transfusions
- Folic acid supplements
- Manage iron deficiency

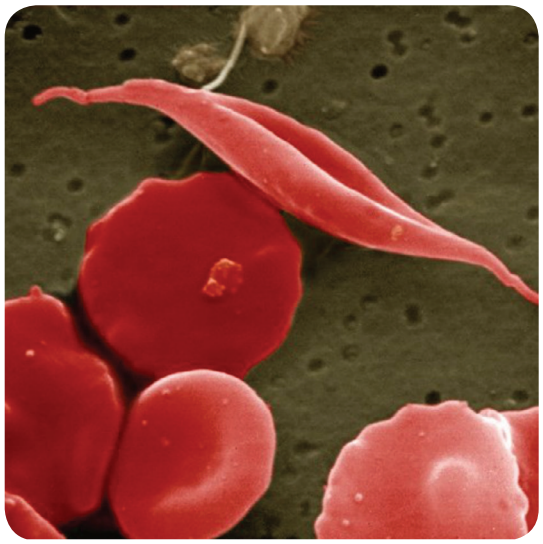

Figure 54.3 A recoloured scanning electron micrograph demonstrating a sickled erythrocyte.

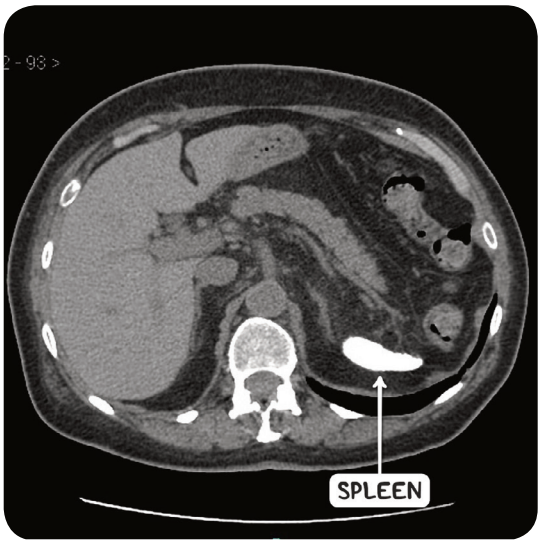

Figure 54.4 An abdominal CT scan in the axial plane demonstrating autosplenectomy in an individual with sickle cell disease. The splenic remnant is densely calcified.

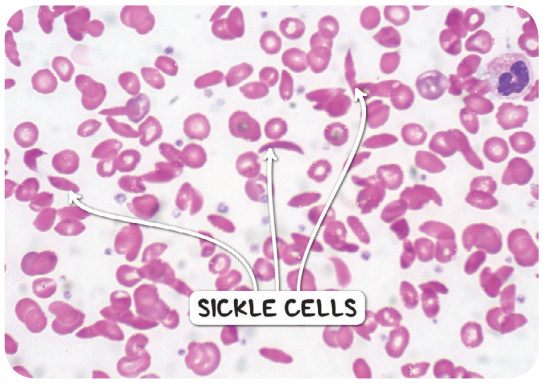

Figure 54.5 A peripheral blood smear containing sickled erythrocytes in an individual with sickle cell disease.