

Hematology and Oncology

Anemia

- Normal red blood cell (RBC) values vary depending on the age of the child (Table 32-1)

Table 32-1. Normal Red Blood Cell Values

Age	HgB (g/dL) Mean (–2SD)	RBC Count ($\times 10^{12}/L$)	MCV (fL)	MCHC (g/%RBC)
0 days	16.5 (13.5)	3.9–5.5	108 (98)	33 (30)
1–3 days	18.5 (14.5)	4.0–6.6	108 (95)	33 (29)
2 wk	16.6 (13.4)	3.6–6.2	105 (88)	31.4 (28.1)
1 mo	13.9 (10.7)	3.0–5.4	101 (91)	31.8 (28.1)
6–8 wk	11.2 (9.4)	2.7–4.9	95 (84)	31.8 (28.3)
3–6 mo	12.6 (11.1)	3.1–4.5	76 (68)	35 (32.7)
6–24 mo	12.0 (10.5)	3.7–5.3	78 (70)	33 (30)
2–6 y	12.5 (11.5)	3.9–5.3	81 (75)	34 (31)
6–12 y	13.5 (11.5)	4.0–5.2	86 (77)	34 (31)
12–18 y				
female	14 (12)	4.1–5.1	90 (78)	34 (31)
male	14.5 (13)	4.5–5.3	88 (78)	34 (31)
18–49 y				
female	14 (12)	4.1–5.1	90 (80)	34 (31)
male	15.5 (13.5)	4.5–5.3	90 (80)	34 (31)

HgB: hemoglobin

MCHC: mean corpuscular hemoglobin concentration

MCV: mean corpuscular volume

RBC: red blood cell

SD: standard deviation

Data source: Nathan DG, Oski FA. *Nathan and Oski's Hematology of Infancy and Childhood*. 6th ed. Philadelphia, Pa: WB Saunders; 2003: 1841, App 11.

- Microcytic anemia
 - Iron deficiency
 - ▶ Reticulocyte count will be low; red cell distribution width (RDW) will be high; serum iron, high total iron binding capacity, and ferritin will be low
 - ▶ Treat with oral (PO) iron (4–6 mg elemental iron/kg daily divided bid or tid); recheck in 6 weeks

- Chronic lead poisoning
 - ▶ Lead prevents normal hemoglobin (Hgb) synthesis
 - ▶ Reticulocyte count will be low, serum lead levels will be high
 - ▶ Treat levels greater than 45 $\mu\text{g}/\text{dL}$ by removing lead exposure and administering DMSA (also called succimer or dimercaptosuccinic acid) tid for 5 days, then bid for 2 weeks or until lead levels are $< 25 \mu\text{g}/\text{dL}$
- Thalassemia
 - ▶ Inherited disorder of Hgb synthesis (see below). May be either α -thalassemia or β -thalassemia, homozygous (severe) or heterozygous (mild)
 - ▶ Use Mentzer index to differentiate between iron deficiency anemia and β -thalassemia
 - ▷ If the result is < 12 , thalassemia is likely
 - ▷ If > 13.5 , iron deficiency is more likely

$$\frac{\text{mean corpuscular volume (MCV)}}{\text{RBC count}}$$

- ▶ Laboratory results for thalassemia will show elevated reticulocyte count, normal RDW, and target cells on smear
- ▶ Treat with folic acid (1 mg PO daily)
 - ▷ Patients with severe cases may need chronic blood transfusions with iron chelators, splenectomy, or both
 - ▷ Do not treat with iron unless iron is depleted
- Chronic inflammation
 - ▶ Inflammation causes iron to be trapped in the reticuloendothelial system
 - ▶ Low reticulocyte counts and mildly increased RDW may also be normocytic
 - ▶ Serum iron and total iron binding capacity will be low, ferritin will be elevated
 - ▶ Treat the underlying disease
- Normocytic anemia
 - Hemolytic
 - ▶ Characterized by premature RBC destruction and elevated reticulocyte count
 - ▶ Smear may show schistocytes, spherocytes, or bite cells
 - ▶ Bilirubin and lactate dehydrogenase levels will be high,

- haptoglobin will be low
- ▶ May need direct antibody testing, osmotic fragility testing, or glucose-6-phosphate dehydrogenase (G6PD) activity; however, G6PD may be normal immediately after an acute attack
 - Acute blood loss
 - Splenic sequestration
 - ▶ Occurs when RBCs become trapped in the spleen
 - ▶ Seen in sickle cell disease or hereditary spherocytosis
 - ▶ Characterized by elevated reticulocyte count and decreased platelet count
 - ▶ Pallor, shock, and enlarged spleen are diagnostic signs
 - ▶ **Treat the shock**; patients in splenic sequestration can rapidly decompensate
 - Transient erythroblastopenia of childhood
 - ▶ Typical age of onset is about 2–3 years
 - ▶ Child is usually pale and tachycardic, but otherwise appears well (may even have a HgB count of 5 g/dL)
 - ▶ Reticulocyte count is low, but MCV is normal before recovery
 - ▶ Observation is usually sufficient treatment
 - ▶ Transfuse only if there are signs of impending cardiovascular collapse
 - Chronic renal disease
 - ▶ Chronic renal disease can cause anemia through a variety of factors, including chronic inflammation, nutritional deficiency or uremia, and decreased erythropoietin
 - ▶ Reticulocyte count and erythropoietin levels will be low
 - ▶ Treat with erythropoietin (50–150 units/kg subcutaneous or intravenous [IV] three times weekly)
 - Macrocytic anemia
 - Vitamin B₁₂ deficiency
 - ▶ Vitamin B₁₂ deficiency is seen in patients with poor diets, poor intestinal absorption, parasites, or bacterial overgrowth
 - ▶ The typical patient has anemia and peripheral neuropathy, though infants may present with tremors, micro-

- ▶ cephalic, developmental regression, and/or failure to thrive
- ▶ Reticulocyte count will be low, neutropenia, and thrombocytopenia may be present, and RDW will be elevated
- ▶ Smear may show hypersegmented neutrophils (≥ 6 lobes)
- ▶ Serum B₁₂ levels may be low
- ▶ Schilling test may be necessary to determine cause
- ▶ Treat with vitamin B₁₂ alone or intrinsic factor
- Folic acid deficiency
 - ▶ Folic acid deficiency can be caused by a nutritional deficit (especially in children drinking goat's milk), poor intestinal absorption (celiac disease), increased body requirements (rapid growth or cell turnover), or metabolic disorders (inborn errors of metabolism or folate antagonistic drugs)
 - ▶ Reticulocyte count will be low, neutropenia, and thrombocytopenia may be present, and RDW will be elevated
 - ▶ Smear may show hypersegmented neutrophils (≥ 6 lobes)
 - ▶ Serum folate levels may be low
 - ▶ If the diagnosis between folic acid and B₁₂ deficiency is unclear and laboratory tests for serum levels are unavailable, give low-dose folic acid (100–500 μg daily)
 - ▷ In folic acid deficiency, reticulocytosis will be seen in 2–4 days; no increase will be seen in B₁₂ deficiency at that dose
 - ▷ Once B₁₂ deficiency is ruled out, treat with folic acid (1 mg PO daily)
- Aplastic
 - ▶ In aplastic anemia, the bone marrow's ability for hematopoiesis is either reduced or completely lacking
 - ▶ Can be a result of acquired or congenital factors
 - ▶ Characterized by low reticulocyte count, pancytopenia, and normal RDW
 - ▶ Bone marrow biopsy and aspiration must be performed
 - ▶ Treatment is supportive with transfusions as needed until a definitive diagnosis is reached
- Bone marrow infiltration
 - ▶ Bone marrow spaces are occupied by tumor, fibrosis, or

- storage disease
 - ▶ Low reticulocyte count, pancytopenia may be present
 - ▶ Bone marrow biopsy and aspiration must be performed
 - ▶ Treatment is supportive with transfusions as needed until a definitive diagnosis is reached
- Liver disease
 - ▶ Shortened RBC survival
 - ▶ Smear will show burr cells or target cells
 - ▶ Prothrombin time (PT)/ activated partial thromboplastin time (aPTT) may be prolonged in more severe liver disease
 - ▶ Treatment is supportive
- Hypothyroidism
 - ▶ Low thyroid hormone down regulates precursor metabolism
 - ▶ MCV may also be normal
 - ▶ Spiculated RBCs are evident on smear
 - ▶ Thyroid function test is consistent with hypothyroidism
 - ▶ Treat the underlying disease
- Dyserythropoiesis / myelodysplastic syndromes
 - ▶ Ineffective erythropoiesis
 - ▶ Presents with a decrease in one cell line that progresses to pancytopenia
 - ▶ Low reticulocyte count
 - ▶ Smear shows teardrop cells
 - ▶ Bone marrow has normal or increased cellularity
 - ▶ Treatment is supportive unless a bone marrow donor is available
- Sickle cell diseases
 - Sickle cell disease occurs frequently in people living in certain parts of Africa, India, and the Middle East; in the United States, it occurs in 0.2% of African Americans
 - It may be detected with a Sickledex (Strek, Inc, Omaha, Neb) or sickle prep solubility test, but the diagnosis is made with HgB electrophoresis
 - ▶ Severe: homozygous sickle HgB disease (HgbSS), HgbS- β^0 -thalassemia
 - ▶ Less severe: a heterozygous sickle HgB disease (eg, HgbSC), HgbS- β^+ -thalassemia

- Complications
 - ▶ 0–4 years old
 - ▷ **Dactylitis/pain crisis:** usually the first clinical manifestation of sickle cell disease
 - The child will present with swollen, tender hands or feet
 - Typically well tolerated and can often be treated with fluids and acetaminophen or nonsteroidal antiinflammatory drugs
 - ▷ **Splenic sequestration:** one of the leading causes of mortality
 - Often complicates sepsis
 - Usually occurs before 2 years of age
 - Patient presents with weakness, left-sided abdominal pain, and progressive shock; a large spleen will be palpated on physical examination
 - Hematocrit will fall to about 50% of the patient's baseline, with an associated drop in platelets; reticulocyte count will be higher than usual
 - **Volume resuscitate first, but patient may need simple or exchange transfusion**
 - Hgb/hematocrit will increase more than is expected as RBCs are released from the spleen
 - Splenectomy will not help during sequestration, but is indicated for patients with recurrent episodes
 - ▷ **Pneumococcal sepsis:** risk is 400-fold in affected children and associated with a 30% mortality rate
 - Child is febrile and appears toxic
 - Admit and treat with appropriate antibiotics based on resistance patterns
 - Prevent with pneumococcal vaccination and penicillin prophylaxis (125 mg PO bid until 3 y, then 250 mg PO bid until at least 5 or 6 y) or erythromycin (10 mg/kg PO bid) for children allergic to penicillin
 - ▶ 4–10 years old
 - ▷ **Stroke:** occurs in about 7% of children; silent infarcts can be seen in up to almost 20%

- Children typically have ischemic strokes (in adults hemorrhagic strokes are more common)
- Diagnosis is made by a noncontrast computed tomography (CT) scan, though a CT scan may be negative in first 3–6 hours
- ▷ **Aplastic crisis:** most often caused by parvovirus B19
 - Infection is more severe in all of the hemolytic anemias because of the shortened life span of the RBC
 - HgB/hematocrit will be lower than baseline, with low or absent reticulocyte count
 - Most cases will resolve on their own, but some patients may need transfusion if reticulocytosis is delayed
- ▷ 10–20 years
 - ▷ **Acute chest syndrome:** second most common cause for hospitalization in sickle cell disease
 - Usually occurs in older children
 - Presents as fever with respiratory symptoms and a new infiltrate on radiography
 - It is more common in the winter with increased upper respiratory infections
 - Mortality rate is 5%
 - More than half of patients with acute chest syndrome have pulmonary fat embolism or an associated infection
 - Treat with: oxygen, incentive spirometry and bronchodilators, analgesics to prevent hypoventilation from pain, and antibiotics to cover atypicals (*Chlamydia* and *Mycoplasma* are common pathogens); hydration can decrease sickling, but overhydration will cause pulmonary edema and worsen the acute chest (typical rate is $\frac{2}{3}$ –1 \times maintenance)
 - Transfuse packed red blood cells (PRBCs) for partial pressure of oxygen (PO_2) $<$ 70 mmHg or worsening pulmonary status; perform exchange transfusion if hematocrit is higher than patient's baseline

- ▶ **Gallstones:** by age 15, more than 40% of children with sickle cell disease have developed cholelithiasis, though they are most often asymptomatic
- ▶ **Priapism:** painful erection lasting for more than 30 minutes
 - Usually occurs in the early hours of the morning or following sexual activity
 - In most cases, it can be treated at home with frequent urination, vigorous exercise, increased fluid intake, and warm baths; if home treatment is unsuccessful after 3 hours, it is unlikely to be effective
 - Hydration, analgesia, and warm compresses may be helpful; if these methods fail within 6–8 hours, PRBC transfusion may be needed, though effect may not be seen for 24 hours
 - If the condition has not begun to resolve 24 hours after PRBC transfusion, surgical consultation is needed for possible shunting to prevent fibrosis and impotence
- ▶ All ages
 - ▶ **Fever:** considered an emergency in all age groups; infection is the most common cause of death in children with sickle cell disease
 - Most patients with sickle cell disease are functionally hyposplenic by 2 years old
 - A patient with a temperature $\geq 38.5^{\circ}\text{C}$ should have a complete blood count (CBC), urinary analysis, and chest radiograph with cultures from the blood, urine, and throat, as well as a broad-spectrum antibiotic that penetrates the central nervous system and covers *Haemophilus influenzae* and *Streptococcus pneumoniae* (eg, ceftriaxone)
 - ▶ **Pain crisis:** the most common manifestation of acute vasoocclusive crisis
 - Most common locations are the lumbosacral spine, hip, femur, knee, shoulder, and elbow
 - Most episodes can be managed at home with increased fluid intake and analgesics, but treat-

- ment with IV morphine (0.1–0.15 mg/kg loading dose) and hydration may be required
- Morphine doses of 5–10 mg are not uncommon, and a history of the patient's prior doses is often most helpful
- Fluids are typically run at $1\frac{1}{2} \times$ maintenance ($D_5\frac{1}{2}NS + 20$ mEq KCl/L)
- Hemolytic anemias
 - The normal RBC lives for about 120 days in circulation. Premature destruction can result in anemia. Patients generally present with anemia, elevated reticulocytosis, and hyperbilirubinemia. Once the diagnosis of hemolytic anemia is made, the cause needs to be determined
 - ▶ Autoimmune hemolytic anemia: group of disorders in which autoantibodies are formed that bind to RBCs and lead to premature destruction
 - ▶ G6PD deficiency: G6PD functions as a reducing enzyme and is found in all cells. The normal half-life of the protein is 60 days. Patients whose G6PD has a shorter half-life are susceptible to hemolysis when RBCs are exposed to oxidative stress
 - ▷ Presentation: G6PD deficiency is predominant in people of African and Mediterranean descent; in these geographical areas, males are more likely to be deficient, although females with G6PD deficiency are not uncommon
 - ▷ Diagnosis: G6PD levels will be normal in the acute phase because all the deficient RBCs will have lysed; once the patient has recovered from the oxidative insult, G6PD levels can be obtained
 - ▷ Treatment: patients should avoid agents that are known to cause hemolysis (most notable is primaquine treatment for malaria)
 - ▷ In the acute phase, patients may require RBC transfusions. Indications for transfusion are:
 - $HgB < 7$ g/dL
 - $HgB < 9$ g/dL with hemoglobinuria
 - ▶ Other causes: there are a host of other causes of hemolysis, including RBC membrane defects (spherocytosis,

elliptocytosis), immune and nonimmune drug-induced hemolysis, and microangiopathy

- Thrombocytopenia

- Thrombocytopenia is defined as a platelet count $< 150,000/\text{mm}^3$. Isolated thrombocytopenia generally does not result in spontaneous bleeding unless the platelet count is less than $30,000/\text{mm}^3$. Trauma or medical procedures may cause increased bleeding in a patient with a platelet count less than $100,000/\text{m}^3$. Thrombocytopenia most commonly results in bleeding of the mucous membranes or the skin (petechiae or bruising)
 - ▶ Immune (idiopathic) thrombocytopenic purpura (ITP): ITP is a common cause of thrombocytopenia in kids
 - ▷ Results when autoantibodies attack platelets
 - ▷ Can be either acute or chronic
 - ▷ Acute ITP occurs most frequently in children between 2 and 8 years old
 - ▷ Presentation: bruising, petechiae, and mucous membrane involvement; splenomegaly is present in only about 10% of patients
 - ▷ Diagnosis: CBC shows a low platelet count, often less than $20,000/\text{mm}^3$, but normal HgB and white blood cell (WBC) counts. Mean platelet volume is frequently elevated. PT/aPTT are normal. Bone marrow aspiration should be considered prior to treating with steroids if the history is not typical, the CBC shows abnormalities beyond thrombocytopenia, or hepatosplenomegaly is present. The aspirate will show increased megakaryocytes. Persistence of ITP for more than 6 months is considered chronic (chronic ITP occurs in 20% of patients with acute ITP)
 - ▷ Treatment of **acute** ITP: can often be treated with observation alone; treat if platelet count is less than $20,000/\text{mm}^3$ with significant mucous membrane bleeding **or** less than $10,000/\text{mm}^3$ with mild purpura
 - Prednisone (4–6 mg/kg/day divided bid, maximum dose of 60 mg/day) tapered in 5–7-day intervals for a total of 21–28 days
 - Methylprednisolone (30 mg/kg/day divided

- bid, maximum dose of 1 g/day) for 3 days for more severe cases
- Anti-D immunoglobulin (50 μ g/kg IV)
 - IV immunoglobulin (0.4 g/kg IV daily) for 5 days, or (1 g/kg IV daily) for 2 days
 - Platelet transfusions should be used only in emergency (eg, surgery, intracranial hemorrhage) because transfused platelets have a very short lifespan
 - Splenectomy is indicated for severe, life-threatening bleeding that is not responsive to medical management
 - Vaccination with meningococcal, pneumococcal, and *H influenzae* b vaccines should be performed, preferably 2 weeks prior to surgery
- ▶ Treatment of **chronic** ITP: evaluate patients for other autoimmune diseases, systemic lupus erythematosus, or human immunodeficiency virus infection; treatment for symptomatic patients is the same as that for acute ITP
- Hemolytic uremic syndrome (HUS)/thrombotic thrombocytopenic purpura (TTP): both conditions are forms of microangiopathic anemia associated with thrombosis. Thrombus formation consumes platelets and hemolyzes RBCs as they pass through the smaller vessels. HUS is often seen in association with *Shigella dysenteriae* or *Escherichia coli* O157:H7 infections. TTP can be seen following viral or bacterial infections, during pregnancy, or with certain drugs
 - ▶ Presentation: gastrointestinal infection, which can include bloody diarrhea; oliguria and hypertension develop early
 - ▷ In TTP, patients initially present with bleeding and neurological symptoms, then later develop fever
 - ▶ Differentiation
 - ▷ Patients with HUS or TTP will have thrombocytopenia and hemolytic anemia, though they are less severe in HUS than in TTP
 - ▷ The platelet count in HUS is greater than 100,000/ mm^3 in half of patients

- ▶ The age of onset for HUS is between 6 months old and 5 years old, whereas TTP is more commonly seen in adults
- ▶ Treatment
 - ▶ HUS treatment should focus on the renal disease with fluid restriction and hypertension management; treat anemia with PRBC transfusions as needed; platelet transfusions are not indicated because life-threatening bleeding is rare and platelet transfusion can worsen thrombosis
 - ▶ Treat TTP with plasmapheresis
- Disseminated intravascular coagulation: an acquired syndrome of intravascular activation of the coagulation cascade that occurs most commonly following sepsis
 - ▶ Presentation: depends upon the underlying disorder
 - ▶ Bleeding, petechiae or mucosal bleeding, or severe hemorrhage may not be present
 - ▶ Patients have prolonged PT/aPTT, decreased fibrinogen, and increased fibrin split products, including D-dimer
 - ▶ Thrombocytopenia is noted on CBC
 - ▶ Treatment: treat the underlying cause and provide replacement therapy
 - ▶ Transfuse platelets to maintain $> 50,000/\text{mm}^3$
 - ▶ Administer fresh frozen plasma (10–15 mL/kg) to maintain prothrombin time $< 2 \times$ normal
 - ▶ Cryoprecipitate to maintain fibrinogen $> 100 \text{ mg/dL}$

Coagulopathies

- Hemophilia A and B are X-linked deficiencies in either factor VIII or factor IX, respectively. The two factors work together to drive the coagulation cascade from the intrinsic pathway to the common pathway
 - Presentation
 - ▶ The two syndromes are clinically identical to each other
 - ▶ Both occur almost exclusively in males
 - ▶ Their first manifestation can be with bleeding at birth or prolonged bleeding after circumcision
 - ▶ Most cases are identified by the time the patient is 18 months old

- ▶ Joint bleeding is the hallmark of hemophilia, with the weight-bearing joints of the legs being most frequently affected
- Evaluation
 - ▶ PT will be normal, but aPTT will be prolonged
 - ▶ A mixing study will correct the defect if the patient has not developed inhibitors
 - ▶ Factor assays will show decreased activity in the factor that is deficient
- Treatment
 - ▶ Factor replacement (Table 32-2)
 - ▶ Patients with mild or moderate factor VIII deficiency can be treated with desmopressin acetate (0.3 µg/kg

Table 32-2. Factor Replacement**

Type of Bleed	Desired Level (%)
Joint or simple hematoma	20–40
Simple dental extraction	50
Major soft tissue bleed	80–100
Head injury (prophylaxis)	100+
Major surgery (dental, orthopaedic, other)	100+

*For factor VIII, each unit/kg will increase level by 2% (eg, to increase from < 10% to 100%, use 50 units/kg).

†For factor IX, each unit/kg will increase level by 1% (eg, to increase from < 10% to 100%, use 100 units/kg).

IV over 15–30 min, or 1 puff [150 µg] intranasally for children < 50 kg, and 2 puffs [300 µg] intranasally for children > 50 kg) if they are known responders

- ▶ **Note:** desmopressin acetate nasal spray for hemophilia is 15-fold the concentration of the spray for diabetes insipidus
- ▶ If specific factors are unavailable, or if the type of hemophilia is not known, fresh frozen plasma can be used (40 mL/kg) because it contains all of the clotting factors
- ▶ Volume overload can be a complication; for patients with hemophilia A, cryoprecipitate (50–100 units factor VII in 10 mL) can be used
- ▶ Patients may develop inhibitors to factors
- Von Willebrand's disease: the most common inherited bleed-

ing diathesis, occurring in 1%–2% of the general population, though in most people, the disease is mild enough that they never seek medical attention

- Presentation: history of easy bleeding or bruising
 - ▶ Bleeding is most often of the platelet type, with epistaxis and mucocutaneous bleeds
 - ▶ Oozing is seen after surgical procedures, especially after dental extractions
 - ▶ Females may have menorrhagia; there is often a family history of the same type of bleeding
- Treatment
 - ▶ Prophylaxis for minor surgery or treatment of minor bleeding with desmopressin
 - ▶ Prophylaxis for major surgery or treatment of significant bleeding with cryoprecipitate, fresh frozen plasma, or platelets (see Chapter 5, Transfusion Medicine, for specifics on using blood products)

Oncology

- The most common malignancies in childhood include leukemia, brain tumors, lymphoma, and neuroblastoma
- Children with cancer are particularly susceptible to infection, which is the primary cause of death in oncology patients
 - This may be due to a deranged or suppressed immune system, poor nutritional status, mucous membrane damage, or indwelling central venous catheters
- In children with fever and neutropenia, initiate broad-spectrum antibiotic therapy with activity against both gram-positive and gram-negative bacteria
 - Carefully search for a source of infection, paying particular attention to mucous membranes, the perineum, and skin surrounding vascular access sites
 - The patient should be admitted until cultures are negative for 48–72 hours, the patient is afebrile for 24–48 hours, and bone marrow shows signs of recovery, with absolute neutrophil count $> 200/\text{mm}^3$ on at least two occasions and rising
 - Antibiotic therapy can be stopped at this time unless a bacterial source is identified

- For fevers that persist for 5 days, or fevers that recur after the patient has been treated for more than 5 days, start antifungal therapy

