Cancer, an uncontrolled proliferation of immature cells, can involve the bone marrow, with resultant abnormalities of peripheral blood cell counts. In leukemia, the most common of the pediatric cancers, the presenting signs and symptoms are a reflection of these events. The most common presenting symptoms are fever, pallor, purpura, and pain. The most common physical examination findings include hepatomegaly, splenomegaly, diffuse lymphadenopathy, and central nervous system (CNS) symptoms. Other common laboratory abnormalities include an increased or decreased total white blood cell count, circulating blasts, elevated lactate dehydrogenase, and elevated uric acid. The onset may be abrupt or chronic. The evolution of symptoms may proceed over a few days, weeks, or months. At first, symptoms may be nonspecific and may mimic other nonmalignant conditions. Fever, particularly if coupled with other nonspecific complaints, may mimic more common pediatric illnesses. Over 70% of children with acute lymphoblastic leukemia (ALL) will present with a platelet count of less than 100,000/μL, of which 20% have less than 20,000/μL. Isolated thrombocytopenia has been reported to be extremely rare in childhood presentation of ALL. A review of the records of 2239 children enrolled in Pediatric Oncology Group or Children’s Cancer Group trials in the 1980s showed that none of these children had significant thrombocytopenia with any other hematologic or physical manifestations of ALL when they were first seen by a hematologist. However, because children previously treated with steroids were excluded from participation in these studies; those children presenting with isolated thrombocytopenia and treated inappropriately for immune thrombocytopenic purpura (ITP) would not have been captured in this data. Similarly, anemia occurs in over 75% of patients ultimately diagnosed with leukemia. The anemia is usually gradual in onset, normocytic, and rarely associated with significant
symptoms. However, isolated anemia, in the absence of other signs or symptoms, is an extremely rare presentation. When confronted with a child or adolescent patient presenting with isolated thrombocytopenia or anemia, the concern for cancer should be minimal if there are no other common signs or symptoms.

THROMBOCYTOPENIA

Neonatal Thrombocytopenia

During fetal life, the platelet count progressively increases and reaches a level of approximately 150,000/µL by the end of the first trimester. Healthy fetuses and neonates at gestational ages of more than 22 weeks have a platelet count within the normal range for adults (150,000–450,000/µL). Thrombocytopenia is a rare occurrence in the general newborn population. When studied prospectively, a platelet count of less than 150,000/µL was found in less than 1% of newborns. However, the incidence among neonates admitted to the neonatal intensive care unit is as high as 35%. The rate of thrombocytopenia in the neonate increases as the gestational age decreases.

In neonates, the underlying cause of thrombocytopenia can often be predicted by the timing of the onset of thrombocytopenia. The natural history of thrombocytopenia is also predictive of causality. Thrombocytopenia in the neonate can be categorized into fetal, early onset (<72 hours of age), and late onset (>72 hours of age). The most common causes of fetal onset thrombocytopenia are alloimmune, congenital infections (such as with cytomegalovirus, Toxoplasma, rubella, and HIV), and aneuploidy (such as trisomies 18, 13, and 21). Less common causes of fetal onset thrombocytopenia are autoimmune, severe hemolytic disease of the newborn, and inherited causes (such as Wiskott-Aldrich syndrome). Because the majority of fetal onset thrombocytopenias present after birth and before discharge from the hospital, only neonatal alloimmune thrombocytopenia (NAIT) is discussed in depth.

NAIT is the platelet equivalent of hemolytic disease of the newborn. NAIT occurs when fetal platelets contain an antigen inherited from the father that is lacking in the mother, resulting in transplacental transfer of maternal IgG antiplatelet antibodies and the ultimate destruction of fetal platelets. Importantly, NAIT can develop in the first pregnancy of an at-risk couple. Because platelet antigens form early in gestation and maternal antibodies cross the placental barrier early in the second trimester, NAIT can result in severe thrombocytopenia. The most common serious side effect of NAIT is intracranial hemorrhage, which can occur in as many as 20% of affected newborns. Nearly 50% of those with intracranial hemorrhage are affected in utero. There is a risk for more severe thrombocytopenia and an increase in the incidence of intracranial hemorrhage in infants affected by NAIT than by autoimmune thrombocytopenia. Antibodies directed against the human platelet antigen-1a (HPA-1a) are responsible for approximately 80% of NAIT in whites. Less than 3% of the white population is homozygous for HPA-1b. HPA-1a incompatibility occurs in 1/150 pregnancies, although thrombocytopenia develops in less than 1/1000 pregnancies. In neonates with NAIT who are neither premature nor ill, thrombocytopenia will resolve in most cases within 1 week without any long-term sequelae. However, in some children, thrombocytopenia lasts for several weeks and may require repeated platelet transfusions. The most important aspect of the management of NAIT is to consider this diagnosis in any case of unexpected severe thrombocytopenia. Prevention of intracranial hemorrhage is an emergency. Term infants who are not ill and have no other risk factors for hemorrhage (eg, traumatic delivery) are transfused using washed and irradiated maternal platelets, or HPA-1a/5b negative platelets, or HPA compatible platelets if available.
in known cases of NAIT. Random donor platelets should only be used if compatible platelets are unavailable. Treatment with intravenous gamma globulin (IVIG) has also been shown to be effective.\textsuperscript{11}

The most common cause of early-onset neonatal thrombocytopenia is fetal hypoxia, such as that associated with pregnancy-induced hypertension, intrauterine growth retardation, and maternal diabetes. Perinatal asphyxia and infection are also common causes. In those neonates with thrombocytopenia with an onset of more than 72 hours after birth, late-onset sepsis, and necrotizing enterocolitis are the most common causes. Less common causes include congenital infection, Kasabach-Merritt phenomenon, metabolic disease, and inherited thrombocytopenia, such as thrombocytopenia with absent radii and congenital amegakaryocytic thrombocytopenia.

**Childhood Thrombocytopenia**

Other than nutritionally acquired anemia, isolated thrombocytopenia, defined as a platelet count of less than 150,000/\mu L, is the most commonly acquired blood disorder in the pediatric population. Thrombocytopenia should be clinically suspected when a child presents with a history of easy bruising or bleeding. Thrombocytopenia can also be discovered incidentally when blood counts are obtained for unrelated reasons. In general, isolated thrombocytopenia can be caused by one of two mechanisms: (1) decreased production of platelets in the peripheral circulation or of the platelet precursor megakaryocytes or (2) increased destruction of platelets or megakaryocytes. Destructive thrombocytopenias can be further classified as either immune-mediated or nonimmune-mediated. Hypersplenism often causes thrombocytopenia. However, hypersplenism is often associated with other cytopenias. Appropriate history taking, physical examination, and judicious use of laboratory testing can lead to an appropriate diagnosis.

The type of bleeding in a particular child can usually be determined by a careful history. Bleeding into deep tissues, joints, or muscles is suggestive of a clotting factor deficiency; such as factor VIII or IX deficiency. Mucosal bleeding, including epistaxis, excessive menstrual bleeding, and gum bleeding, suggests either a quantitative or qualitative platelet disorder. In children with bleeding symptoms and a normal platelet count, functional platelet disorders and hereditary hemorrhagic telangiectasia must be considered.\textsuperscript{12} A detailed history of medication use is essential, as a number of medications can affect both platelet count and platelet function. Recent vaccinations or a history of repeated infections are important, as both could contribute to thrombocytopenia.\textsuperscript{13} Finally, a family history of bleeding or thrombocytopenia is important because the child may have inherited disorders such as von Willebrand disease, dysfibrinogenemias, Wiskott-Aldrich syndrome, or Bernard-Soulier syndrome.

A variety of signs and symptoms of systemic disease, found on physical examination, are often present in the child with thrombocytopenia. Mucocutaneous bleeding from the mouth, nose, gastrointestinal tract, or uterus, particularly following a recent viral illness, is most likely the result of acute ITP. Thrombocytopenia associated with signs, symptoms, and laboratory features of autoimmune disease, such as lupus or rheumatoid arthritis, is often indicative of chronic ITP. Splenomegaly from any cause can result in thrombocytopenia. The presence of extensive lymphadenopathy suggests the presence of a lymphoid malignancy. Skeletal abnormalities are associated with congenital thrombocytopenias. The presence of hemangiomas may be associated with Kasabach-Merritt phenomenon and resultant thrombocytopenia.

Laboratory evaluation of isolated thrombocytopenia begins with a complete blood count, including evaluation of the peripheral blood smear. Large platelets seen on
peripheral smear suggests a platelet destructive state, such as that seen in ITP. Giant platelets and mild thrombocytopenia associated with major platelet dysfunction is suggestive of Bernard-Soulier syndrome. Thrombocytopenia associated with small platelet size, especially when associated with eczema and immunodeficiency, can be suggestive of Wiskott-Aldrich syndrome. The presence of red blood cell fragments, even if anemia is not present, could be an indication of a serious systemic illness, such as hemolytic uremic syndrome (HUS), thrombotic thrombocytopenic purpura (TTP), or disseminated intravascular coagulation (DIC). Low fibrinogen or the presence of fibrin degradation products, such as elevated d-dimer, suggests a consumptive disorder, such as that seen with hemangiomas associated with Kasabach-Merritt phenomenon. The combination of anemia, leukopenia, and thrombocytopenia (also known as pancytopenia) is suggestive of general bone marrow dysfunction or a bone marrow infiltrative process and warrants further evaluation, including bone marrow examination.

If the history and physical examination do not support the laboratory finding of thrombocytopenia, confirmation that the thrombocytopenia is not an artifact or laboratory error is essential. Improper specimen collection or handling is known to cause platelet clumping resulting in pseudothrombocytopenia. Ethylenediamine-tetraacetic acid-dependent antibodies have also been shown to cause pseudothrombocytopenia.14

**Thrombocytopenia Secondary to Platelet Destruction**

Thrombocytopenia as a result of ongoing platelet destruction can often be determined on peripheral blood smear by the presence of very large platelets. The bone marrow compensates for the platelets being destroyed by releasing younger, larger, more reactive platelets.15 In this setting, the bone marrow sample will usually show normal or increased numbers of megakaryocytes. The most common cause of thrombocytopenia in childhood is because of an increased destruction of an immune-mediated mechanism.

**Immune thrombocytopenic purpura**

ITP usually occurs in children between the ages of 2 and 4 years, although it has been described at birth and into adulthood.16 Typically the child is affected by the sudden onset of petechiae, purpura, ecchymoses, bruises, epistaxis, hematuria, or gastrointestinal hemorrhage. Importantly, the child with ITP is usually in good health. There is often a history of antecedent viral illness.11 In over 80% of children with ITP, the disease is acute, self-limited, and resolves within 6 months. If thrombocytopenia persists for more than 6 months, the condition is referred to as chronic ITP. Chronic ITP is more common in children older than 10 years and in those younger than 1 year.

Isolated thrombocytopenia with normal white and red blood cell counts is the laboratory hallmark of ITP. In certain cases, bleeding can lead to anemia at the time of diagnosis. If multiple autoantibodies are present, patients may also have an autoimmune hemolytic anemia and, in rare cases, neutropenia. The combination of two autoimmune cytopenias is referred to as Evan syndrome. Review of the peripheral blood smear is important to ensure the presence of normal white blood cell morphology and differential and normal red blood cell morphology. The presence of any other abnormality on peripheral smear would suggest an alternate diagnosis.

The treatment of childhood ITP is controversial. There is no consensus as to whether “watchful waiting” or pharmacologic intervention is most appropriate.17 No randomized trials have compared observation and pharmacologic therapy on the outcome of children with ITP. Pharmacologic therapy does not reduce the risk for
developing chronic ITP. It remains unclear if pharmacologic therapy reduces the risk for life-threatening bleeding because of the low prevalence rate of such adverse events. Both the American Society of Hematology and British Society of Hematology have published guidelines for the management of ITP in children based on expert opinions and observational studies.

Regardless of whether pharmacologic therapy is used, restriction of activity should be recommended in all children with ITP. In addition, medications with antiplatelet activity, including the nonsteroidal anti-inflammatory drugs, should be avoided.

The standard pharmacologic therapeutic options for childhood ITP include corticosteroids, IVIG, or intravenous anti-D immune globulin. In randomized trials of children with ITP, prednisone therapy has been shown to more rapidly increase platelet counts than placebo. A variety of dosing regimens have been shown to be effective in raising a patient’s platelet count, ranging from 2 mg/kg/d for 21 days, to 30 mg/kg of methylprednisolone daily for 4 days, to high dose- short course oral dexamethasone at 20 mg/m²/d for 4 days. There is no evidence that any one regimen is most effective. Repeat courses may be given in patients with persistent, recurrent, or chronic disease. Although most patients respond to corticosteroids with an increase in platelet count, a decrease in platelet count after the discontinuation of steroid therapy is not unusual. Side effects of corticosteroid therapy include behavioral change, sleep disturbance, increased appetite, and weight gain. Although rare, acute leukemia can present with isolated thrombocytopenia, even in the absence of other signs of systemic illness. For this reason, the empiric use of corticosteroids for childhood acute ITP is not recommended, unless a bone marrow examination has been performed to ensure that the patient does not have leukemia.

The use of IVIG for the therapy of childhood acute ITP was first reported in 1981. The mechanism of IVIG is unknown, though it is thought to be multifactorial and to involve the competitive inhibition of autoantibody adsorption of the patient’s platelets, prevent the reticuloendothelial uptake of autoantibody-coated platelets, and interact with the autoantibodies with anti-idiotype antibodies in the IVIG preparation. Regardless of the mechanism, IVIG has been shown to be superior to corticosteroids or no treatment in improving platelet numbers in patients with ITP. As with corticosteroids, various dosing regimens have been reported. A single dose of 1000 mg/kg has been shown to increase platelet count in 24 hours. The most common side effect of IVIG therapy includes flu-like symptoms, with fever, headache, and nausea. The cost of a single course of IVIG is significantly greater than that of corticosteroid therapy.

Life-threatening bleeding in the child with acute ITP is rare. Intracranial hemorrhage (ICH) has an incidence of less than 0.5%. The presence of significant headache should prompt careful evaluation for any other neurologic signs. Early diagnostic imaging should be considered to identify ICH. If ICH or other life-threatening hemorrhage occurs, immediate intervention should be given which includes platelet transfusion (the only indication for platelet transfusion in ITP), IVIG at 1000 mg/kg daily for 2 days, and methylprednisolone at 30 mg/kg intravenously daily for at least 3 days. Additionally, emergency splenectomy may be considered.

**Kasabach-Merritt phenomena**

The association between thrombocytopenia and hemangiomas during infancy is often accompanied by evidence of consumption of coagulation factors. Kasabach-Merritt phenomenon seems to be more common in children with kaposiform hemangioendothelioma and tufted hemangiomas. Regression of the hemangiomas achieved through surgery, medical therapy, or time usually results in the resolution of the thrombocytopenia.
Medication toxicity
A variety of medications have been shown to cause thrombocytopenia. Depending on the agent, the mechanism of the thrombocytopenia can be bone marrow suppression, drug-antibody immune complexes, or development of antibodies to platelet antigens exposed by way of drug-platelet interactions. Heparin-induced thrombocytopenia (HIT) in childhood is becoming recognized more commonly.²⁸ Rather than causing bleeding, HIT is associated with thrombosis.

Hemolytic uremic syndrome
The combination of renal failure, thrombocytopenia, and microangiopathic hemolytic anemia is often associated with a diarrheal illness. Laboratory evaluation will reveal schistocytes and polychromatophilia on the peripheral smear, anemia, an elevated serum level of lactate dehydrogenase, and renal insufficiency. A related disorder, TTP also includes CNS changes in the constellation of symptoms.

Infections and disseminated intravascular coagulation
Thrombocytopenia can occur as part of generalized activation of the coagulation cascade in DIC. Infections can also lead to thrombocytopenia independent of DIC.

Thrombocytopenia Secondary to Decreased Production
Decreased production of platelets can be secondary to bone marrow infiltration by disorders such as acute leukemia, storage diseases, myelofibrosis, granulomatous disorders, or histiocytosis. In the vast majority of cases, children affected by these disorders will have more than one cell line affected. Similarly, thrombocytopenia may be present in generalized bone marrow aplasias, either congenital or acquired (such as Fanconi anemia or idiopathic aplastic anemia).

Hereditary amegakaryocytosis
This condition is usually associated with skeletal abnormalities. Thrombocytopenia with absent radii (TAR) is such a syndrome. In this condition, both upper and lower limb defects are present. Most commonly, radial agenesis is seen. Bone marrow examination is remarkable for the absence of megakaryocytes with normal red blood cell and white blood cell precursors. Fortunately, affected children require platelet transfusions only until 1 year of age, by which time there is usually spontaneous recovery of platelet production.

Congenital idiopathic amegakaryocytic thrombocytopenia
This is a diagnosis of exclusion. These infants present in a similar manner to those affected by TAR. The thrombocytopenia does not resolve spontaneously. A defect in the c-mpl gene has been associated with this condition.²⁹

Bernard-Soulier syndrome
Platelets of individuals with autosomal recessive Bernard-Soulier syndrome lack glycoprotein 1b, the platelet receptor for von Willebrand factor. The thrombocytopenia is mild and the platelets are large, in the range of red blood cells. Bleeding is usually only seen around the time of invasive procedures or trauma. Treatment is usually supportive, but can include antifibrinolytics, platelet transfusions, and recombinant factor VIIa. The cause of the thrombocytopenia is not known. Other macrothrombocytopenias include gray platelet syndrome and May-Hegglin anomaly.

Wiskott-Aldrich syndrome
Of particular importance to emergency physicians and pediatricians because of the associated immune dysregulation and serious infections, Wiskott-Aldrich syndrome
is an X-linked recessive disorder in which children have thrombocytopenia with small platelets, severe eczema, and recurrent infections. Supportive care is important. Hematopoietic cell transplantation is curative.

ANEMIA

Anemia is defined as a reduction in red blood cell mass or blood hemoglobin concentration. In practice, these are most often signaled by reductions of either the hemoglobin, a measure of the concentration of hemoglobin in whole blood expressed as grams per 100 mL (dL), or hematocrit, the fractional volume of a whole blood sample occupied by red blood cells. The age variation for the hemoglobin and hematocrit varies widely in the pediatric population. It is particularly important to use age and sex adjusted norms when evaluating a pediatric patient for anemia. In addition, there is racial variation, with healthy black children having an average hemoglobin value 0.5 g/dL, which is less than that of white children of the same age and sex.

Although anemias have typically been classified on a morphologic basis (based on red blood cell size), classifying anemias physiologically affords a more intuitive approach to the child with anemia. Using this approach, anemias can be broken down into the following categories (Table 1):

- Anemia resulting from an inability to adequately produce red blood cells
- Anemia resulting from excessive red blood cell destruction
- Anemia resulting from excessive blood loss

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Physiologic causes of anemia</th>
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<tr>
<td><strong>Inability to Produce Red Blood Cells</strong></td>
<td><strong>Destruction of Red Blood Cells</strong></td>
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<tr>
<td>Transient erythroblastopenia of childhood</td>
<td>Intrinsic defects</td>
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<tr>
<td>Diamond-Blackfan anemia</td>
<td>• Membranopathies</td>
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<td>Iron deficiency anemia</td>
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<td>Infections</td>
<td>• Paroxysmal nocturnal hemoglobinuria</td>
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<td>• Hepatitis A</td>
<td>• Enzyme deficiencies</td>
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<td>• Hepatitis B</td>
<td>• Pyruvate kinase</td>
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<td>• Hepatitis C</td>
<td>• Glucose-6-phosphate dehydrogenase</td>
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<td>• Epstein-Barr virus</td>
<td>• Hexokinase</td>
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<td>• Human immunodeficiency virus</td>
<td>• Anti-glucose-6-phosphate isomerase</td>
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<td>• Parovirus B19</td>
<td>• Hemoglobinopathies</td>
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<td>Anemia of chronic disease</td>
<td>• Sickle cell anemia</td>
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<td>• Thalassemia</td>
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<td><strong>Extrinsic defects</strong></td>
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<td></td>
<td>• Autoimmune hemolytic anemias</td>
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<td>• Hemolytic uremic syndrome</td>
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<td></td>
<td>• Thrombotic thrombocytopenic purpura</td>
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<td></td>
<td>• Kasabach-Merritt phenomenon</td>
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Evaluation of the reticulocyte count aids in defining the etiology of anemia. An increased reticulocyte count generally is seen as a normal bone marrow response to ongoing red blood cell destruction or loss. A decreased reticulocyte count, which reflects decreased production of red blood cells, is most consistent with bone marrow depression.

The clinical signs and symptoms of anemia vary based on the age of the child and the etiology and chronicity of the anemia. When evaluating the history of a patient with anemia, one must not only review the symptoms of the patient, but also ask questions regarding family history, birth history, and neonatal course, as all these may provide important etiologic clues. Common symptoms of anemia include lethargy, tachycardia, and pallor. Infants with anemia may present with irritability and poor oral intake. In contrast, patients with chronic anemia may be well compensated and may have no significant medical concerns. The following components should be part of the history when evaluating a child with suspected anemia:

- Severity and initiation of symptoms
- Questions relating to hemolytic episodes, such as change in urine, skin, or sclera color and the gender of the affected child (some hemolytic anemias, such as glucose-6-phosphate dehydrogenase (G6PD) deficiency, are X-linked).
- History of prior anemic episodes, including duration, etiology, resolution, and prior therapies
- Questions about possible blood loss including bleeding from the gastrointestinal tract, bleeding from the urinary tract, and epistaxis. In adolescent females, a detailed menstrual history is important.
- Prior drug or toxin exposure
- Questions relating to diet including those aimed at determining iron content in the diet
- Family history, race, and ethnicity

The physical examination may also provide important clues as to the etiology of the anemia. Pallor should be assessed by examining sites where capillary beds are visible through the mucosa (eg, conjunctiva, palms, and nails). Mild to severe anemia can be missed when relying solely on these physical findings. Patients with hemolytic processes resulting in anemia may present with signs of jaundice and hepatosplenomegaly resulting from increased red blood cell destruction.

The laboratory examination of suspected anemia should begin with a complete blood count, a reticulocyte count, and a review of the peripheral smear by an individual skilled at red blood cell morphology. If hemolytic anemia is suspected, a direct antiglobulin test (direct Coombs) should also be done.

**Anemia Due to Decreased Red Blood Cell Production**

The most common pediatric anemias caused by decreased production of red blood cells in the bone marrow are transient erythroblastopenia of childhood (TEC) and Diamond-Blackfan anemia (DBA). Both are considered pure red blood cell aplasias. TEC is acquired, whereas DBA is congenital. Both present during early childhood with signs and symptoms of anemia. Laboratory evaluation shows reticulocytopenia.

**Transient erythroblastopenia of childhood**

TEC was first described in 1970 as a temporary red cell aplasia occurring in previously healthy children, secondary to a temporary cessation of erythropoiesis. Etiologies include preceding viral infections, inhibitors against erythroid progenitor cells, and cell-mediated suppression of erythropoiesis. In approximately
half of cases, children have a history of viral illness in the preceding 2 or 3 months. TEC is usually seen in children older than 6 months. Unlike some children with DBA, those with TEC are otherwise clinically normal. On presentation, patients generally have anemia in the range of 6 to 8 g/dL and exhibit reticulocytopenia. Mild neutropenia may be present. Platelet count is generally in the normal range or slightly elevated. In contrast to patients with DBA, patients with TEC do not have an elevated red blood cell mean corpuscular volume (MCV) at diagnosis. Neither do they have an increased percentage of hemoglobin F or expression of i antigen. Previous hemoglobin concentration measurements in patients with TEC, if obtained, are normal. Distinguishing between DBA and TEC patients who present with hypoplastic anemia in the first year of life may be particularly challenging. Many times, these patients do not have a previously documented blood count. Their erythrocytes may have residual fetal characteristics (eg, i antigen and increased hemoglobin F). Following the MCV in children presenting with hypoplastic anemia in the first year of life may help to differentiate between these two entities. Occasionally, examination of the bone marrow is necessary to differentiate the two clinical entities. The typical clinical course of TEC consists of 1 to 2 months’ disease duration followed by complete recovery. Decisions regarding whether a child with TEC requires red blood cell transfusion is based purely on a child’s clinical presentation. If the child affected by TEC is experiencing minimal symptoms secondary to the anemia, no transfusion of packed red blood cells is necessary. Steroids have no role in the treatment of TEC.

**Diamond-Blackfan anemia**

DBA was first described as a congenital hypoplastic anemia with the following features:

- Progressive normochromic, usually macrocytic anemia in infancy or early childhood
- Reticulocytopenia
- Normal cellularity of the bone marrow with marked decrease or absent erythroid precursors
- Normal or slightly decreased white blood cell count and normal or slightly increased platelet count

Over 90% of children with DBA present within the first year of life, with 35% diagnosed within the first month. The pathogenesis of DBA is uncertain. Erythropoietin production is normal in children with DBA. Antibodies to erythropoietin have not been described. Up to 50% of children with DBA have associated congenital abnormalities. These findings occur mainly in the head and upper limbs and include the following:

- Craniofacial abnormalities
- Neck anomalies
- Thumb abnormalities
- Genitourinary malformations
- Prenatal and postnatal growth failure

Abnormal laboratory findings in DBA consist of anemia, which is usually macrocytic. The anemia is frequently profound at diagnosis, with a mean hemoglobin concentration of 4.0 g/dL in infants presenting at older than 2 months of age. Patients usually have an increased percentage of hemoglobin F for their age and their red blood cells
have increased expression of the i antigen. Bone marrow examination shows normal overall cellularity with decreased or absent erythroid precursors. Red blood cell adenosine deaminase activity is elevated in patients with DBA. The mainstays of therapy for DBA are corticosteroids and red blood cell transfusions. The response rate to corticosteroids has ranged from 50% to 75%. Steroid responsiveness is associated with older age at presentation, a family history of DBA, and a normal platelet count at the time of diagnosis. Transfusion therapy is the treatment of choice for patients who do not respond to steroids. The major complication of long-term transfusion therapy is hemosiderosis, which may result in significant morbidity and mortality. Bone marrow transplantation has been done successfully in steroid refractory patients.

**Iron deficiency anemia**

Iron deficiency is the most common nutritional deficiency in children. The World Health Organization estimates that anemia, largely caused by iron deficiency, affects between 500 million and 2 billion people worldwide. In some developing countries, up to 50% of preschool children and pregnant mothers have iron deficiency anemia (IDA). In the United States, the prevalence of IDA among children has been declining as a result of improved iron supplementation.

Neonates of mothers with iron deficiency are at increased risk for IDA in early infancy. During the first 5 to 6 months of life, the normal term infant is iron replete. However, several conditions in the newborn period can lead to the development of IDA:

- Prematurity
- The administration of erythropoietin for anemia of prematurity
- Fetal-maternal hemorrhage
- Twin-twin transfusion syndrome
- Other perinatal hemorrhagic events
- Insufficient dietary intake

Premature infants are at increased risk for IDA in early infancy because of a smaller total blood volume at birth, increased loss through phlebotomy, and poor gastrointestinal absorption.

Dietary issues contribute significantly to the evolution of IDA in infancy and early childhood. Common factors leading to IDA include the following:

- Insufficient iron intake
- Decreased absorption because of poor dietary sources of iron
- Early introduction of whole cow’s milk
- Occult blood loss secondary to cow’s milk intolerance
- Medications
- Malabsorption states

Recommendations for the prevention of iron deficiency in infants include the following:

- Encourage breast-feeding for the first 4 to 6 months; after this time, consider adding iron-fortified cereals. Two or more servings a day meet an infant’s requirement for iron.
- For breast fed preterm or low-birth weight infants, begin iron supplementation (1 to 2 mg/kg/d) at 1 month and continue until 12 months.
- For infants younger than 12 months of age who are not breast-fed or are partially breast-fed, use only iron-fortified formulas.
At 6 months of age, encourage one feeding per day of foods rich in vitamin C. After 6 months of age, or when developmentally ready, consider introducing pureed meats, which increase the absorption of nonheme iron. Avoid low-iron formulas or cow’s milk until 12 months of age. Children aged 1 to 5 years should consume no more than 600 mL (20 oz) of milk daily. They should consume an adequate amount of iron-containing foods to meet daily requirements.

The most common presentation of IDA is an otherwise asymptomatic, well-nourished infant or child who has a mild to moderate microcytic, hypochromic anemia. Much less frequent are infants with severe anemia, who present with lethargy, pallor, irritability, cardiomegaly, poor feeding, and tachypnea. Although typically presenting as a nutritional anemia, IDA may present as part of a complex medical problem that includes gastrointestinal blood loss, malabsorption syndromes, and chronic inflammatory diseases. Other clinical manifestations include the following:

- Impaired psychomotor and mental development is well described in iron-deficient infants. Cognitive impairment may occur in adolescents.
- Iron deficiency in children has been associated with mild to moderate defects in leukocyte and lymphocyte function.
- Moderately severe IDA is associated with decreased work capacity, in part because iron is an essential cofactor for enzyme-driven aerobic metabolism. Decreased iron, in the absence of anemia, has been associated with decreased exercise performance in adolescent athletes.
- Pica, an appetite for substances not fit for food, is found in children with iron deficiency, even in the absence of anemia. It responds rapidly to treatment with iron.
- IDA has been reported to be associated with cerebral vein thrombosis.

For infants presenting with a mild microcytic anemia and a presumptive diagnosis of IDA, the most cost-effective strategy is a therapeutic trial of oral iron supplementation. Ferrous sulfate (3–6 mg/kg of elemental iron, once or twice daily between meals) should produce a rise of more than 1 g/dL in patients with IDA. Other laboratory tests that may help confirm the diagnosis of IDA include the following:

- An elevated red blood cell distribution width is the earliest hematologic manifestation of iron deficiency.
- Iron deficiency in infants and young children can be identified by a serum ferritin concentration of less than 12 mg/mL.
- For children unresponsive to oral iron supplementation, a more complete laboratory evaluation would include serum iron, total iron binding capacity, and transferrin saturation.

For infants with confirmed IDA, ferrous sulfate (3–6 mg/kg/d of elemental iron) remains the standard therapy. Iron-fortified formulas and iron supplementation at these doses are infrequent causes of gastrointestinal symptoms. In children with severe IDA, a reticulocyte response may be seen within 72 hours.

If a child does not respond to adequate oral iron supplementation, potential causes for refractory IDA include the following:

- Failure to adhere to recommendations
- Intolerance to medication
Ongoing gastrointestinal blood loss
Chronic inflammatory disease
Pulmonary hemosiderosis
Incorrect diagnosis

Rarely is parenteral iron supplementation required. Even less common is the need for red blood cell transfusion.

*Other anemias that result from decreased red blood cell production*

Multiple infectious agents have been associated with the development of red blood cell aplasia, including hepatitis A, B, and C; Epstein-Barr virus; and HIV. However, parvovirus infection is most commonly associated with acquired red blood cell aplasia.\(^{50}\) Human parvovirus B19 infection results in erythema infectiosum (Fifth disease) in childhood. The virus has been long associated with aplastic crisis in patients with hemolytic anemias and, infrequently, transient aplasia in an otherwise healthy child.\(^{51}\) Parvovirus infection of red blood cell precursors expressing the P antigen receptor results in temporary cessation of red blood cell production. In patients who have normal red blood cell turnover, this cessation may be of insignificant consequence. However, in patients who have a concurrent active hemolytic process (eg, sickle cell anemia or hereditary spherocytosis); the temporary cessation of red blood cell production may result in severe anemia, also known as an aplastic crisis. In general, these crises are self-limiting and resolve within 2 weeks. During the period of aplasia, children may also have a decrease in the white blood cell and platelet counts. Children with immunocompromised states, including HIV infection, are at risk for developing chronic anemia with parvovirus infection because of the inability to clear the viral infection.\(^{52}\) The diagnostic workup for children suspected of having a parvovirus infection may include serum titers for parvovirus IgM and IgG, and detection of the virus via polymerase chain reaction from either bone marrow or peripheral blood. Children with chronic hemolysis who present with parvovirus-induced aplasia generally have resolution of the anemia in a short period, and only require transfusions based on clinical symptoms caused by the anemia. Immunosuppressed children may benefit from therapy with IVIG. Other bone marrow failure syndromes, such as aplastic anemia and Fanconi anemia, which usually affect granulocytes and platelets in addition to red blood cells, may present with isolated anemia. Malignancy and myelofibrosis may also result in bone marrow replacement, causing anemia with a poor reticulocyte response.

Erythropoietin (EPO) is the growth factor responsible for the regulation of red blood cell production. EPO is produced primarily in the kidneys. Children with chronic renal disease are known to have anemia that is largely caused by decreased EPO levels. Therapy with pharmacologic doses of EPO has been proven effective in resolving anemia in this population.\(^{53}\) Other causes of decreased EPO levels include surgical removal of the pituitary gland, hypothyroidism, and starvation.

Anemia of chronic disease (ACD) is multifactorial and is usually associated with the presence of infection, inflammation, or malignancy. ACD is usually a mild anemia with normal-sized red blood cells and reticulocytopenia. The presence of normal or elevated ferritin concentrations serves to distinguish ACD from IDA, in which ferritin concentrations are minimal. Most patients with ACD require no specific therapy. Correcting the underlying condition will result in an increase of the hemoglobin concentration.

*Anemia Due to Increased Red Blood Cell Destruction*

In the steady state, approximately 1% of the circulating red blood cells are destroyed daily. They are replaced by an equal number of new cells released from the bone
marrow (reticulocytes). In compensation for a reduced red blood cell lifespan, the bone marrow increases its output of reticulocytes. A hemolytic process can be measured indirectly by the presence of increased levels of the metabolic products of hemolysis (e.g., increased indirect bilirubin, increased lactate dehydrogenase, and reduced haptoglobin). Even in the presence of elevated unconjugated bilirubin, overt clinical jaundice may be absent or missed. Hemolytic disorders may be classified according to whether the shortened erythrocyte survival is a result of an intrinsic abnormality of the red blood cell or extrinsic abnormality acting on a normal red blood cell. These two categories are not necessarily mutually exclusive because some hemolytic disorders are caused by a combination of intrinsic and extrinsic mechanisms.

**Intrinsic hemolytic anemias**

Intrinsic hemolytic anemias generally result from inherited abnormalities of the red blood cell membrane, intracellular enzymes, or hemoglobin. Although the red blood cell membrane disorders are caused by different molecular defects, they have a similar pathophysiology. The typical features of red blood cell membrane disorders, such as hereditary spherocytosis (HS), are of a familial hemolytic anemia with varying degrees of severity, splenomegaly, and morphologically abnormal red blood cells seen on peripheral blood smear. In the case of HS, the red blood cells are spherocytes. A deficiency or abnormality of red blood cell membrane structural proteins, such as spectrin in HS, results in an accelerated loss of the red blood cell membrane, reducing red blood cell surface area. Because there is no concomitant loss of cellular volume, the red blood cells assume a spherical shape. The spleen is intrinsically involved in the hemolytic process because the splenic circulation imposes a metabolic stress on the abnormal red blood cells. The spherocyte is rigid and nondeformable. As it passes through the spleen, the spherocyte is sequestered and destroyed. The hemolytic process regresses after splenectomy, but the biochemical and morphologic abnormalities persist. The red blood cell membrane abnormalities may present in the neonatal period with anemia and hyperbilirubinemia that may require phototherapy or exchange transfusion. Anemia varies considerably in severity but tends to be similar within the same family. Indicators of hemolysis include reticulocytosis, anemia, and hyperbilirubinemia. Hemoglobin usually ranges from 6 to 10 g/dL. The reticulocyte count can range from 5% to 20%. The spherocytic red blood cells are smaller than normal red blood cells and lack the central pallor of the biconcave disk. Only a relatively small proportion of the cells are spherocytic. Abnormality of the red blood cell can be shown by osmotic fragility studies. Splenectomy can produce a clinical cure, but should be deferred until the child is at least 5 years old. If the anemia is severe enough to impair growth or normal activity, the procedure can be considered earlier in life. Splenectomy prevents gallstones and eliminates the threat of aplastic crisis. After splenectomy, jaundice and reticulocytosis disappear. The hemoglobin concentration normalizes, although the spherocytosis and osmotic fragility abnormalities become more pronounced. Overwhelming sepsis after splenectomy occurs less frequently if the surgery is delayed until the child is 5 years old. However, the febrile, asplenic child must always be carefully and urgently evaluated for sepsis. Immunization with polyvalent pneumococcal and meningococcal vaccine should be completed at least 2 weeks before splenectomy. Some authorities advocate prophylactic penicillin therapy after splenectomy, especially if the splenectomy is performed before the child is 6 years of age.

Paroxysmal nocturnal hemoglobinuria (PNH) is a rare chronic anemia with prominent intravascular hemolysis that may have its onset in late childhood. Hemolysis is characteristically worse during sleep, with morning hemoglobinuria present. The
primary defect in PNH resides in an abnormal surface protein anchor to the red blood cell membrane. This extracellular anchor, glycosylphosphatidylinositol, is missing from all cells of patients affected with PNH. In addition to chronic hemolysis, thrombocytopenia and leukopenia may develop. Some cases have been followed by aplastic anemia, myelodysplasia, or acute leukemia. The diagnosis is established by the failure to identify CD55 or CD59 on the surface of white or red blood cells. Infections tend to trigger hemolysis. Therapy is supportive and symptomatic. Hematopoietic cell transplantation has been a successful therapy.

Most anemias resulting from abnormalities of red blood cell glycolytic enzymes are inherited in an autosomal recessive manner. The diagnosis is established by showing reduction of the enzyme activity. Deficiencies of glycolytic enzymes compromise adenosine triphosphate generation. The metabolic energy requirements of the red blood cells cannot be met; therefore the red blood cell lifespan is shortened.

An inherited deficiency of pyruvate kinase (PK) is the most common of the red blood cell enzyme deficiencies. A broad spectrum of clinical and hematologic findings occurs in the child affected by homozygous PK deficiency ranging from a mild, compensated hemolytic state to severe anemia. Anemia and hyperbilirubinemia may occur in the neonatal period. In the older patient, pallor, scleral icterus, and splenomegaly are usual findings. The blood smear shows polychromatophilic red blood cells, an indication of an elevated reticulocyte count. No spherocytes are found. Osmotic fragility is normal. Hyperbilirubinemia in the neonatal period may require exchange transfusion. Severe disease may require repeated transfusions for anemia during infancy and childhood. Splenectomy, although not curative, may improve the anemia and should be considered in patients with severe disease. Marked reticulocytosis occurs after splenectomy.

G6PD deficiency results in two kinds of hematologic problems: (1) a common acute condition manifested by hemolytic episodes induced by infection or certain drugs, or (2) a rare chronic nonspherocytic anemia.

The G6PD gene is found on the X chromosome. G6PD is crucial for protection of the red blood cell from oxidant stress. In G6PD deficiency, oxidant metabolites of numerous drugs result in denaturation and precipitation of hemoglobin, which results in red blood cell injury and rapid hemolysis. The degree of hemolysis varies with the drug’s antioxidant effect, the amount ingested, and the severity of the enzyme deficiency. Hemoglobinemia and hemoglobinuria occur 24 to 48 hours after the ingestion of oxidant substances. The hemoglobin level may decrease acutely to less than 5 g/dL. Bite cells can be observed during the acute phase. Spontaneous recovery is usually indicated by reticulocytosis and an increase in hemoglobin concentration. Diagnosis depends on direct or indirect reduction of G6PD activity in red blood cells. By direct measurement, enzyme activity in affected people is less than 15% of normal. Shortly after a hemolytic event, and at a time when a reticulocyte response has occurred, G6PD activity may be normal, secondary to the fact that G6PD activity is higher in reticulocytes. A repeat examination several weeks later, when the reticulocytosis has subsided, may be necessary to confirm the diagnosis. Prevention of hemolysis by avoiding oxidant drugs is of paramount importance. After hemolysis has occurred; supportive therapy, including blood transfusions if the anemia is severe and the child is symptomatic, is indicated.

Deficiencies of several other glycolytic red blood cell enzymes have been described in children with congenital nonspherocytic hemolytic anemias. They include deficiencies of hexokinase, glucose-6-phosphate isomerase, phosphofructokinase, aldolase, triosephosphate isomerase, glyceraldehyde-3-phosphate isomerase, and
phosphoglycerate kinase. These diseases are extremely rare and most are transmitted as autosomal recessive traits. Some are associated with neurologic disease, metabolic myopathy, and abnormal glycogen metabolism. Chronic hemolysis, often manifested in infancy, is a common feature. Specific red blood cell morphologic abnormalities are not seen. Diagnosis depends on the reduction of the specific red blood cell enzyme. No specific therapy exists for these conditions. Splenectomy may reduce the rate of hemolysis in some, but not all, of these disorders.

**Extrinsic hemolytic anemias**

Agents that damage erythrocytes may lead to their premature destruction. The most clearly defined of these agents are antibodies directed against specific intrinsic membrane antigens that damage the red blood cell and produce hemolysis. The most important feature of this disease is the positive Coombs antiglobulin test, which detects immunoglobulins (IgM or IgG) or components of complement on the red blood cell surface. In autoimmune hemolytic anemias (AIHA), circulating antibodies are directed against the child’s own erythrocytes. The factors evoking such an autoimmune response are unknown, but include viral infections and occasionally specific drugs. AIHAs associated with an underlying disease process such as lymphoma, lupus, or immunodeficiency, are said to be secondary. In idiopathic AIHA, no such underlying disease exists. AIHAs occur in 2 clinical patterns. The first type occurs in infants and young children and is frequently preceded by a respiratory infection. The onset is acute, with pallor, jaundice, and hemoglobinuria. The spleen is enlarged. A consistent response to corticosteroid therapy, low mortality, and complete recovery are characteristic. No underlying disease is found. A second type of AIHA has a prolonged course and a significant mortality. Underlying diseases, such as systemic autoimmune conditions and cancers, are frequently found.

The anemia associated with AIHA may be severe, with hemoglobin concentrations of less than 6 g/dL. Spherocytosis and polychromasia are prominent. Reticulocytosis and nucleated red blood cells are present. The white blood cell and platelet count are usually normal. Occasionally, concomitant ITP occurs (Evan syndrome). The direct and indirect antiglobulin (Coombs) test are positive, indicating the presence of antibodies attached to the red blood cells or free in the serum, respectively. In acute, transient cases, only complement is found on the red blood cells. Transfusion may be required, but offers only transient benefit. Completely compatible blood is difficult to find. Transfusing blood that is incompatible as judged by the cross match is often necessary. Prednisone should be administered in a dose of 2 to 4 mg/kg/d. Treatment should continue until hemolysis decreases. The dose can then be gradually reduced. The acute form of the disease usually remits spontaneously within a few weeks or months, but the antiglobulin test may remain positive for an extended period of time. Splenectomy and immunosuppressive agents may be beneficial in patients refractory to conventional therapy.

Cold antibodies, antibodies that bind to red blood cells most efficiently at temperatures below 36°C, may exist normally, but may increase to very high levels after some viral or mycoplasmal infections. These high titers of cold antibodies induce intravascular hemolysis with resulting hemoglobinemia and hemoglobinuria. The antibodies are of the IgM class and require complement for activity. Spontaneous agglutination and rouleaux formation are seen on the blood smear. Patients with infectious mononucleosis may develop acute hemolytic anemia. The antibodies in these cases have anti-I specificity.
SUMMARY

Isolated cytopenias, particularly anemia and thrombocytopenia, are a common reason to visit the pediatric emergency department. Unless seen in combination with other common signs and symptoms of cancer, isolated anemia or isolated thrombocytopenia is an uncommon presentation for an underlying malignancy. Neonatal thrombocytopenia is most commonly secondary to maternal antibody that has crossed the placenta and is still circulating in the infant’s bloodstream. During childhood, although there is a broader differential diagnosis, most cases of isolated thrombocytopenia are also immune mediated. Anemias can be a result of the problems in red blood cell production, increased red blood cell destruction, or blood loss. If an emergency department practitioner requires assistance with sorting out the cause of anemia or thrombocytopenia in a child or adolescent, consultation with the pediatric hematology department would be recommended.

REFERENCES