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Thrombocytopenia in Infants and Children

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Objectives After completing this article, readers should be able to:

1. Explain the relationship between platelet count and bleeding risk.
2. State the two basic underlying pathologic mechanisms that may lead to clinically significant thrombocytopenia.
3. Describe the typical presentation and natural history of immune (idiopathic) thrombocytopenic purpura (ITP) in children.
4. List the features of the complete blood count and peripheral blood smear that suggest a serious disorder associated with decreased platelet production.
5. Discuss the treatment modalities that have been proven to be effective in raising the platelet count to a safe level in children who have ITP and are experiencing significant bleeding manifestations.

Introduction

Platelets are essential for maintaining the integrity of the vascular endothelium and controlling hemorrhage from small-vessel injury through the formation of platelet plugs (primary hemostasis). More extensive injury and involvement of larger blood vessels requires, in addition to platelets, the participation of the coagulation system to provide a firm, stable, fibrin clot (secondary hemostasis). Thrombocytopenia, defined as a platelet count of less than $150 \times 10^3 / \mu\text{L}$ ($150 \times 10^9 / \text{L}$), is the most common cause of defective primary hemostasis that can lead to significant bleeding in children.

Thrombocytopenia should be suspected when a child presents with a history of easy bruising or bleeding, particularly mucosal or cutaneous bleeding. However, the most common office presentation of a patient who has isolated thrombocytopenia is the unexpected discovery of a low platelet count when a complete blood count (CBC) is obtained for unrelated reasons.

Thrombocytopenia can be caused by one of two mechanisms: decreased production of platelets or increased destruction or removal of platelets from the circulation. Management of thrombocytopenia should be guided by an understanding of its cause and clinical course. The principal management goal in all patients who have thrombocytopenia is to maintain a safe platelet count to prevent significant bleeding. What constitutes a safe platelet count in a specific patient varies, depending on the cause of the thrombocytopenia and consideration of all other aspects of hemostasis, as well as the patient's expected level of activity.

Platelet Count and Bleeding Risk

Platelets are nonnucleated, cellular fragments produced by the megakaryocytes of the bone marrow. As the megakaryocyte matures, the cytoplasm fragments, and large numbers of platelets are released into the circulation. Once released, the life span of platelets is about 7 to 10 days, after which they are removed from the circulation by cells of the monocyte-

Abbreviations

CBC:	complete blood count
DIC:	disseminated intravascular coagulation
HIV:	human immunodeficiency virus
HUS:	hemolytic-uremic syndrome
ICH:	intracranial hemorrhage
Ig:	immunoglobulin
IGIV:	immune globulin intravenous
ITP:	immune thrombocytopenic purpura
KMS:	Kasabach-Merritt syndrome
MPV:	mean platelet volume
NAIT:	neonatal alloimmune thrombocytopenia
NEC:	necrotizing enterocolitis
PBS:	peripheral blood smear
SLE:	systemic lupus erythematosus
TTP:	thrombotic thrombocytopenic purpura
WAS:	Wiscott-Aldrich syndrome

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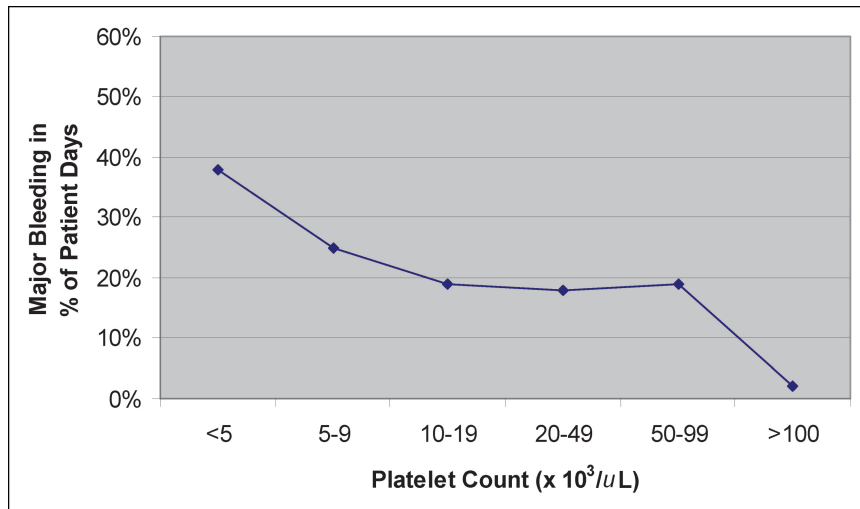


Figure 1. Relationship between major bleeding and platelet count. Adapted from Slichter SJ. Relationship between platelet count and bleeding risk in thrombocytopenic patients. *Transfus Med Rev.* 2004;18:153–167.

macrophage system. In disorders characterized by increased platelet destruction and shortened platelet life span, a healthy marrow may increase platelet production over the basal rate by about tenfold.

Circulating platelets perform many critical hemostatic functions. When small blood vessels are transected, platelets accumulate at the site of injury, forming a hemostatic plug. Platelet adhesion is initiated by contact with extravascular components, such as collagen, and facilitated by the presence and binding of von Willebrand factor. Secretion of mediators of hemostasis (eg, thromboxane, adenosine 5' diphosphate, serotonin, and histamine) cause firm aggregation via fibrinogen binding and increase local vasoconstriction. Platelets also are necessary for normal clot retraction. Bleeding risk increases with a low platelet count.

The normal platelet count ranges from 150 to $450 \times 10^3/\mu\text{L}$ (150 to $450 \times 10^9/\text{L}$). The risk of bleeding does not increase until the platelet count falls significantly below $100 \times 10^3/\mu\text{L}$ ($100 \times 10^9/\text{L}$) (Fig. 1). (1) A platelet count greater than $50 \times 10^3/\mu\text{L}$ ($50 \times 10^9/\text{L}$) is adequate for hemostasis in most circumstances, and patients who have mild thrombocytopenia will likely never be recognized unless a platelet count is obtained for other reasons. Patients who have moderate thrombocytopenia, with platelet counts between 30 and $50 \times 10^3/\mu\text{L}$ (30 and $50 \times 10^9/\text{L}$) are rarely symptomatic (ie, easy bruising or bleeding), even with significant trauma. Patients who have persistent platelet counts between 10 and $30 \times 10^3/\mu\text{L}$ (10 and $30 \times 10^9/\text{L}$) are

often asymptomatic with normal everyday activities but may be at risk for excessive bleeding with significant trauma. Spontaneous bleeding typically does not occur unless platelet counts are less than $10 \times 10^3/\mu\text{L}$ ($10 \times 10^9/\text{L}$). Such patients commonly have petechiae and spontaneous bruising, but even they may be entirely asymptomatic. In most cases, it appears that the platelet count must be less than $5 \times 10^3/\mu\text{L}$ ($5 \times 10^9/\text{L}$) to cause critical spontaneous bleeding (eg, atraumatic intracranial hemorrhage [ICH]). (1)

Younger circulating platelets are larger and more hemostatically active. Thus, patients who have destructive thrombocytopenias accompanied by a brisk production

and release of younger platelets have less severe bleeding symptoms than patients who have a similar degree of thrombocytopenia due to impaired platelet production, resulting in an older circulating population of platelets.

Causes of Thrombocytopenia

The system used most often to categorize the different causes of thrombocytopenia is based on the underlying pathologic mechanism leading to the thrombocytopenia, that is, either increased destruction or decreased production of platelets (Table 1).

Increased Destruction

Disorders involving increased destruction or removal of platelets from the circulation typically result in the appearance of enlarged platelets on the peripheral blood smear (PBS), indicating that the bone marrow is producing new platelets to compensate for the increased destruction. In this setting, examination of the bone marrow generally shows normal or increased numbers of megakaryocytes. The destructive mechanisms resulting in thrombocytopenia are:

- Immune-mediated destruction
- Platelet activation and consumption
- Mechanical platelet destruction
- Platelet sequestration and trapping

IMMUNE-MEDIATED DESTRUCTION. The most common cause of thrombocytopenia due to increased de-

Table 1. Causes of Thrombocytopenia

Increased Platelet Destruction

- Immune-mediated
 - Immune thrombocytopenic purpura
 - Neonatal alloimmune thrombocytopenia
 - Neonatal autoimmune thrombocytopenia
 - Autoimmune diseases
 - Drug-induced
- Platelet activation/consumption
 - Disseminated intravascular coagulation
 - Hemolytic-uremic syndrome
 - Thrombotic thrombocytopenic purpura
 - Kasabach-Merritt syndrome
 - Necrotizing enterocolitis
 - Thrombosis
- Mechanical platelet destruction
- Platelet sequestration
 - Chronic liver disease
 - Type 2B and platelet-type von Willebrand disease
 - Malaria

Decreased Platelet Production

- Infection
- Cyanotic congenital heart disease
- Bone marrow failure or infiltrate
 - Acute lymphoblastic leukemia and other malignancies
 - Acquired aplastic anemia
 - Fanconi pancytopenia
- Nutritional deficiencies
- Genetically impaired thrombopoiesis
 - Thrombocytopenia with absent radii syndrome
 - Congenital amegakaryocytic thrombocytopenia
 - Wiskott-Aldrich syndrome
 - X-linked thrombocytopenia with thalassemia
 - Giant platelet disorders
 - Bernard-Soulier syndrome
 - May-Hegglin/Fechtners/Epstein and Sebastian syndromes

struction of platelets in infants and children is an immune-mediated process. Autoantibodies, drug-dependent antibodies, or alloantibodies may mediate platelet destruction through interaction with platelet membrane antigens, leading to increased platelet clearance from the circulation.

Primary ITP is an acquired immune-mediated disorder characterized by isolated thrombocytopenia in the absence of any obvious initiating or underlying cause. (2)(3) Formerly, the abbreviation ITP stood for idiopathic thrombocytopenic purpura. The new terminology reflects the current understanding of the immune-

mediated nature of the disease and the absence or minimal signs of bleeding in most cases. The platelet count now used to define cases of ITP is less than $100 \times 10^3 / \mu\text{L}$ ($100 \times 10^9 / \text{L}$). (2) The term secondary ITP refers to immune-mediated thrombocytopenias that are due to an underlying disease or to drug exposure. (2)(3) The distinction between primary and secondary ITP is clinically relevant both in regard to prognosis and treatment.

ITP is the most common immune-mediated thrombocytopenia in children, with an annual incidence of symptomatic cases estimated to be between 3 and 8 cases per 100,000 children. Pediatric patients who develop ITP usually present between the ages of 2 and 10 years, with a peak incidence at 2 to 5 years. There does not appear to be a significant sex bias in childhood ITP. (4)(5)

The typical case of symptomatic childhood ITP is characterized by the sudden appearance of bruising or mucocutaneous bleeding in an otherwise healthy child, often after a preceding viral illness. An increased risk of ITP is also associated with measles, mumps, rubella immunization, which accounts for perhaps 50% of all ITP cases during the second year after birth. This form of ITP tends to be transient and rarely is the bleeding severe.

The history should reveal no systemic symptoms such as fever, weight loss, or bone pain. Other than mucocutaneous bleeding, patients should appear well. No lymphadenopathy or hepatosplenomegaly should be present. If one or more of these findings are present, another diagnosis should be strongly considered. Otherwise, the diagnosis of ITP can be made based on two criteria: 1) isolated thrombocytopenia with otherwise normal blood counts and PBS and 2) no clinically apparent associated conditions that may cause thrombocytopenia.

The severity of bleeding symptoms in childhood ITP is proportionate to the degree of thrombocytopenia. Serious bleeding requiring transfusion is uncommon. The presenting platelet count is usually less than $20 \times 10^3 / \mu\text{L}$ ($20 \times 10^9 / \text{L}$). This value probably is due to patients who have higher platelet counts, which are much less likely to lead to bleeding, never coming to medical attention. Children who have ITP and platelet counts greater than $30 \times 10^3 / \mu\text{L}$ ($30 \times 10^9 / \text{L}$) usually have few or no symptoms and require no treatment other than restriction of activity and avoidance of medications that have antiplatelet or anticoagulant activity. For those whose platelet counts are below $30 \times 10^3 / \mu\text{L}$ ($30 \times 10^9 / \text{L}$), treatment recommendations are based on the presence and severity of associated bleeding symptoms or the risk thereof. (4)(6)

ITP is now classified by duration into newly diagnosed, persistent (3- to 12-month duration), and chronic (>12-month duration). (2)(3) Whereas ITP in adults typically has an insidious onset and follows a chronic course, ITP in children is usually short-lived, with about two thirds of patients making full and sustained recoveries within 6 months of presentation, with or without treatment. (2)(3) Children who have persistent or chronic ITP or who manifest any atypical features should be referred to or discussed with a hematologist experienced in the assessment and treatment of children who have ITP.

Neonatal alloimmune thrombocytopenia (NAIT) is an uncommon syndrome whose estimated incidence in the general population is 1 in 1,000 to 5,000 births. The condition is manifested by an isolated, transient, but potentially severe thrombocytopenia in the neonate due to platelet destruction by maternal alloantibodies. NAIT occurs when fetal platelets contain an antigen inherited from the father that the mother lacks. Fetal platelets that cross the placenta into the maternal circulation trigger the production of maternal immunoglobulin (Ig) G antiplatelet antibodies against the foreign antigen. These antibodies recross the placenta into the fetal circulation and destroy the body's platelets, resulting in fetal and neonatal thrombocytopenia (analogous to hemolytic disease of the newborn). In contrast to Rh sensitization, NAIT often develops in the first pregnancy of an at-risk couple. The most serious complication of NAIT is ICH, which occurs in approximately 10% to 20% of affected newborns, with up to 50% of these events occurring in utero. (7) The mother of a newborn who has NAIT is asymptomatic, although she may have a history of previously affected pregnancies. Affected newborns typically present with signs consistent with severe thrombocytopenia, including petechiae, bruising, and bleeding, but are otherwise healthy. Platelet counts are often less than $10 \times 10^3 / \mu\text{L}$ ($10 \times 10^9 / \text{L}$). The platelet count typically falls in the first few days after birth, but then rises over the next 1 to 4 weeks as the alloantibody concentration declines. In families who have an affected infant, the rate of recurrence is as high as 75% to 90%, and thrombocytopenia in the second affected child is always as or more severe than in the first. (7)

Neonatal autoimmune thrombocytopenia also can occur. This disorder is mediated by maternal antibodies that react with both maternal and infant platelets. This pathologic mechanism occurs in maternal autoimmune disorders, including ITP and systemic lupus erythematosus (SLE). The diagnosis usually is apparent from the mother's medical history and maternal thrombocytopenia.

Mothers of infants who manifest unexplained neonatal thrombocytopenia should be investigated for the presence of an autoimmune disorder because neonatal thrombocytopenia can sometimes be the presenting sign of maternal disease. Clinical signs are consistent with isolated thrombocytopenia, as in NAIT.

The risk of severe thrombocytopenia and ICH is greater in alloimmune than in autoimmune neonatal thrombocytopenia. Ninety percent of infants born to mothers who have ITP have safe ($>50 \times 10^3 / \mu\text{L}$ [$50 \times 10^9 / \text{L}$]) or normal platelet counts. (8) The risk for severe thrombocytopenia in the infant generally correlates with the severity of ITP in the mother. Neonatal thrombocytopenia may be predicted if the mother has had a splenectomy for treatment of chronic refractory ITP, the mother's platelet count has been less than $50 \times 10^3 / \mu\text{L}$ ($50 \times 10^9 / \text{L}$) at some time during the pregnancy, or an older sibling has had neonatal thrombocytopenia. (8) Platelet counts of infants born to mothers who have ITP often decrease sharply during the first several days after birth. The nadir typically occurs at 2 to 5 days of age, and infants should be monitored closely during this time. (8)

Autoimmune diseases such as SLE can present in childhood with isolated immune-mediated thrombocytopenia, and the true diagnosis may not be apparent for a prolonged period of time. Autoimmune diseases occur more commonly in older children and have an insidious onset of symptoms and persistent thrombocytopenia beyond 6 months from the time of presentation. Infrequently, other autoimmune-mediated cytopenias present coincidentally with thrombocytopenia. In particular, Evans syndrome is characterized by a Coombs (direct antiglobulin test)-positive hemolytic anemia in association with immune-mediated thrombocytopenia. Antibody-mediated thrombocytopenia also occurs with antiphospholipid antibody syndrome and autoimmune lymphoproliferative syndrome.

Drug-induced thrombocytopenia is a rare cause of thrombocytopenia in children. Medications begun within the past month are more likely to be the cause of the thrombocytopenia than medications that have been taken for longer periods of time. Drug-induced thrombocytopenia is typically caused by drug-dependent antibodies formed against a new antigen on the platelet surface that is created by drug binding to a platelet surface protein. Heparin-induced thrombocytopenia, which can be associated with severe thrombosis, is due to the formation of antibodies against the heparin-platelet factor 4 complex. The platelet count in heparin-induced thrombocytopenia is usually only moderately decreased.

Although this condition is more commonly seen in adults, heparin-induced thrombocytopenia has been described in children. Other drugs commonly used in pediatrics that can cause thrombocytopenia include carbamazepine, phenytoin, valproic acid, trimethoprim/sulfamethoxazole, and vancomycin. Support for the diagnosis of drug-induced thrombocytopenia is provided by resolution of the thrombocytopenia within approximately 1 week of withdrawal of the offending drug.

PLATELET ACTIVATION AND CONSUMPTION. In patients who experience disseminated intravascular coagulation (DIC) and the microangiopathic disorders hemolytic-uremic syndrome (HUS) and thrombotic thrombocytopenic purpura (TTP), thrombocytopenia occurs because of systemic platelet activation, aggregation, and consumption (Table 2). More localized platelet activation and consumption contributes to the thrombocytopenia seen in Kasabach-Merritt syndrome (KMS), necrotizing enterocolitis (NEC), and thrombosis in infants and neonates. In infants who have KMS, thrombocytopenia results from shortened platelet survival caused by sequestration of platelets and coagulation activation in large vascular malformations of the trunk, extremities, or abdominal viscera. Cutaneous vascular lesions are noted at birth in approximately 50% of patients. Detection of visceral lesions requires imaging studies. All patients have severe thrombocytopenia, hypofibrinogenemia, elevated fibrin degradation products, and fragmentation of red blood cells on PBS.

NEC is a syndrome of gastrointestinal necrosis that occurs in 2% to 10% of infants whose birthweights are less than 1,500 g. Thrombocytopenia is a frequent finding and can result in significant bleeding. In the early stages of NEC, declining platelet counts correlate with the presence of necrotic bowel and worsening disease. The primary mechanism of thrombocytopenia appears to be platelet destruction, although the destruction is not caused by laboratory-detectable DIC in most cases. Thrombosis in infants and neonates is often accompanied by thrombocytopenia. A thromboembolic disorder should be considered if the thrombocytopenia cannot be explained by other conditions.

MECHANICAL PLATELET DESTRUCTION. The use of extracorporeal therapies, such as extracorporeal membrane oxygenation, cardiopulmonary bypass, hemodialysis, and apheresis, is associated with mechanical destruction of platelets, which may result in thrombocytopenia. Exchange transfusion also may reduce platelet number by loss in the exchange effluent. Severe ongoing hemor-

rhage requiring rapid and repeated red blood cell transfusions may lead to thrombocytopenia due to a “wash out” phenomenon.

PLATELET SEQUESTRATION AND TRAPPING. About one third of the platelet mass is normally sequestered in the spleen at any given time. A greater proportion of platelets are sequestered in patients who experience hypersplenism, reducing the number of circulating platelets and leading to thrombocytopenia. The survival of platelets in persons who have hypersplenism is normal or near normal. It is the pooling and unavailability of platelets “trapped” in the spleen that is the problem. Leukopenia or anemia also may accompany a low platelet count caused by hypersplenism. Conditions in this category include:

- Chronic liver disease with portal hypertension and congestive splenomegaly. Occasionally, isolated thrombocytopenia may be the initial manifestation of this type of chronic liver disease. The platelet count is typically in the range of 50 to $100 \times 10^3 / \mu\text{L}$ (50 to $100 \times 10^3 / \text{L}$) and usually does not represent a clinically important problem.
- Type 2B and platelet-type von Willebrand disease. Thrombocytopenia in this disorder is caused by increased removal of platelets from the circulation. Increased binding between larger von Willebrand factor multimers and platelets leads to the formation of small platelet aggregates that are cleared from the circulation, resulting in a lower platelet count.
- Malaria with hypersplenism. This diagnosis should be considered in any child who has fever, splenomegaly, thrombocytopenia, and a history of recent travel to an endemic area.

Decreased Production

Impaired platelet production may be due to loss of bone marrow space from infiltration, suppression or failure of cellular elements, or a defect in megakaryocyte development and differentiation. In this setting, examination of the bone marrow generally shows decreases in the number of megakaryocytes. Causes of marrow dysfunction include:

- Infection
- Cyanotic heart disease
- Bone marrow failure or infiltration
- Nutritional deficiencies
- Genetic defects

Table 2. Disorders of Systemic Platelet Activation and Consumption

	Pathophysiology	Clinical Features	Diagnosis	Treatment	Prognosis
Disseminated intravascular coagulation (DIC)	<p>Pathologic activation of coagulation mechanisms, resulting in extensive microvascular thrombosis leading to ischemia and end-organ damage.</p> <p>Consumption of platelets and coagulation factors and activation of fibrinolysis result in hemorrhage.</p>	<p>Complication of underlying illnesses such as sepsis, asphyxia, meconium aspiration, severe respiratory distress syndrome, extensive trauma.</p> <p>Symptoms include bleeding, hypotension, increased vascular permeability, and shock.</p>	<ul style="list-style-type: none"> Thrombocytopenia Fragmented RBCs Prolonged PT, aPTT Decreased plasma fibrinogen Increased FDPs 	<p>Only effective therapy is reversal of underlying cause.</p> <p>Temporizing measures include:</p> <ul style="list-style-type: none"> Platelet transfusions for bleeding, severe thrombocytopenia FFP to replenish coagulation and antithrombotic factors 	<p>Varies, depending on the underlying disorder and the extent of the intravascular thrombosis but regardless of cause is often grim, with 10% to 50% mortality.</p>
Hemolytic-uremic syndrome (HUS)	<p>Most cases preceded by episode of bloody diarrhea due to verotoxin-producing <i>Escherichia coli</i> O157H7.</p> <p>Verotoxin enters bloodstream, attaches to glomerular endothelium, and inactivates the metalloprotease ADAMTS13, responsible for cleaving very large multimers of vWF. Uncleaved vWF initiates platelet aggregation and activation, resulting in network of microthrombi in kidneys that lead to fragmentation of RBCs, consumption of platelets, and tissue ischemia.</p> <p>Less common form without diarrhea possibly due to factor H deficiency with uncontrolled complement activation and thrombosis after minor endothelial injury.</p>	<p>Seen predominantly in children. Usually preceded by episode of bloody diarrhea.</p> <p>Onset of illness characterized by pallor and oliguria with thrombocytopenia and laboratory evidence of microangiopathic hemolytic anemia and ARF.</p>	<ul style="list-style-type: none"> Thrombocytopenia Fragmented RBCs Increased BUN, creatinine Normal PT, aPTT Normal plasma fibrinogen Normal FDPs 	<p>Supportive care.</p> <p>Dialysis, as needed, until evidence of recovering renal function.</p> <p>Antibiotic treatment not recommended because it may stimulate further verotoxin production.</p> <p>Platelet transfusions may worsen outcome.</p> <p>If diagnostic uncertainty between HUS and TTP because of neurologic or other nonrenal involvement, plasma exchange recommended.</p>	<p>Mortality rate is 5% to 10%. Most survivors recover without major consequences. Small proportion of patients develops chronic renal insufficiency.</p>
Thrombotic thrombocytopenic purpura (TTP)	<p>Most commonly associated with inhibition of ADAMTS13 by autoantibodies. As in HUS, without proper cleavage of vWF, in TTP, a network of microthrombi in multiple organ systems results in clinical and laboratory findings. Rarer form called Upshaw-Schüliman syndrome is a genetically inherited dysfunction of ADAMTS13.</p>	<ul style="list-style-type: none"> Thrombocytopenia Microangiopathic hemolytic anemia ARF Neurologic symptoms Fever <p>ARF and neurologic symptoms may not be present initially. Fever uncommon. Only thrombocytopenia and microangiopathic hemolytic anemia without other apparent cause required to suspect diagnosis.</p>	<ul style="list-style-type: none"> Thrombocytopenia Fragmented RBCs Elevated LDH Increased BUN, creatinine Normal PT, aPTT Normal plasma fibrinogen Normal FDPs Decreased (<5% of normal) ADAMTS13 activity Detectable inhibitors of ADAMTS13 	<p>Daily plasma exchange using FFP reduces anti-ADAMTS13 antibodies and replenishes concentrations of the enzyme. May be needed for 1 to 8 weeks before laboratory values normalize.</p> <p>Upshaw-Schulman syndrome patients receive FFP every 2 to 3 weeks to maintain adequate concentrations of functioning enzyme.</p>	<p>Mortality rate ~95% for untreated cases but 10% to 20% for patients treated early with plasma exchange.</p> <p>Approximately 30% of patients experience a relapse within 10 years of the first attack.</p>

aPTT=activated partial thromboplastin time, ARF=acute renal failure, BUN=blood urea nitrogen, FDP=fibrin degradation product, FFP=fresh frozen plasma, LDH=lactate dehydrogenase, PT=prothrombin time, RBC=red blood cell, vWF=von Willebrand factor

INFECTION. Thrombocytopenia due to infections not associated with evidence of DIC is usually caused by bone marrow suppression. In some cases, increased destruction due to an infection-induced immune-mediated process or splenomegaly and reticuloendothelial hyperactivity may compound the problem of bone marrow suppression. The most common infectious agents associated with thrombocytopenia due to bone marrow suppression are Epstein-Barr virus, cytomegalovirus, parvovirus, varicella virus, and rickettsiae. In most cases, the thrombocytopenia is transient, with recovery within a period of weeks. Thrombocytopenia is a common finding in patients who are infected with the human immunodeficiency virus (HIV), in whom both platelet destruction and impaired production appear to play roles in decreasing the platelet count.

CYANOTIC HEART DISEASE. Cyanotic congenital heart disease is associated with thrombocytopenia. The cause is unclear, but the mechanism appears to involve decreased production of megakaryocytes.

BONE MARROW FAILURE OR INFILTRATION. Thrombocytopenia associated with anemia and leukopenia (ie, pancytopenia) suggests general bone marrow dysfunction or infiltration. Serious disorders such as leukemia or other malignancy, hemophagocytic lymphohistiocytosis, acquired aplastic anemia, myelodysplasia, and inherited bone marrow failure syndromes such as Fanconi pancytopenia syndrome and dyskeratosis congenita can present with pancytopenia. General bone marrow dysfunction can also be caused by exposure to chemotherapeutic agents or radiation.

Acute lymphoblastic leukemia is the most common childhood leukemia. Affected children usually have other clinical and laboratory findings besides thrombocytopenia. These manifestations include systemic symptoms such as fever, bone pain, and weight loss as well as hepatosplenomegaly, lymphadenopathy, leukocytosis, and anemia.

Acquired aplastic anemia is a rare disorder caused by profound, almost complete bone marrow failure. Specific symptoms associated with acquired aplastic anemia vary but can include fever, fatigue, dizziness, weakness, headaches, and episodes of excessive bleeding. Pancytopenia is often seen on presentation. Based on the response of approximately 50% of patients to immunosuppressive medications, including antithymocyte globulin, cyclosporine, high-dose corticosteroids, and cyclophosphamide, most cases are now believed to be due to an

immune-mediated destruction of hematopoietic stem cells.

Fanconi pancytopenia syndrome is a rare autosomal recessive disorder. The mean age at diagnosis of the pancytopenia is approximately 6 to 9 years, but the condition may be recognized earlier by characteristic congenital malformations that are present in 60% to 70% of affected patients. The most common malformations are hypopigmented macules, café-au-lait macules, abnormalities of the thumbs, microcephaly, and urogenital abnormalities. Short stature of prenatal onset may also be seen.

NUTRITIONAL DEFICIENCIES. Folate, vitamin B12, and iron deficiencies have been associated with thrombocytopenia. Folate and vitamin B12 deficiencies impair bone marrow production, usually resulting in pancytopenia. Iron deficiency, which can cause either thrombocytosis or thrombocytopenia, appears to impair a late stage of thrombopoiesis. Thrombocytosis and iron deficiency may be a response to gastrointestinal blood loss.

GENETIC CAUSES OF IMPAIRED THROMBOPOIESIS. A large number of rare inherited diseases present with reduced platelet count, and many involve impaired platelet function as well. These conditions arise from genetic defects of the megakaryocyte lineage that result in impaired thrombopoiesis. The consideration of congenital thrombocytopenia should be greater in patients who have a prolonged history of asymptomatic abnormal platelet counts or a family history of thrombocytopenia. Some patients born with congenital thrombocytopenia are followed for many years with the presumptive diagnosis of ITP until another family member is discovered to have a low platelet count. Table 3 outlines the genetic causes of impaired thrombopoiesis.

Clinical Manifestations

Children who have thrombocytopenia may be asymptomatic or symptomatic. In asymptomatic patients, thrombocytopenia is often detected unexpectedly on a CBC obtained for another clinical issue. Symptomatic patients generally present with mucosal or cutaneous bleeding.

Mucosal bleeding usually manifests as epistaxis, gingival bleeding or extensive oral mucous membrane bleeding (“wet purpura”), hematuria, or in postpubertal females, excessive menstrual bleeding. The presence of “wet purpura” is widely perceived as a risk factor for potentially life-threatening hemorrhage.

Cutaneous bleeding usually appears as petechiae or

Table 3. Genetic Causes of Impaired Thrombopoiesis

Diagnosis	Inheritance	Cause	Clinical Features	Laboratory Features	Prognosis	Treatment
Thrombocytopenia with absent radii syndrome	Variable inheritance	Unclear genetic cause. Possible defect of megakaryocyte maturation. Does not involve either thrombopoietin or thrombopoietin receptor.	<ul style="list-style-type: none"> Severe thrombocytopenia Bilateral absent radii Normal thumbs Other skeletal, genitourinary, heart anomalies 	<ul style="list-style-type: none"> Absent or markedly decreased megakaryocytes Normal erythroid and myeloid maturation 	<p>Mortality significant in infancy due to intracranial hemorrhage. If patient survives, thrombocytopenia often improves over next several years.</p> <p>Often progresses to pancytopenia and leukemic transformation</p>	<ul style="list-style-type: none"> Platelet transfusions
Congenital amegakaryocytic thrombocytopenia	Autosomal recessive	Mutations in thrombopoietin receptor gene, leading to absent or dysfunctional thrombopoietin receptors.	<ul style="list-style-type: none"> Severe but isolated thrombocytopenia 	<ul style="list-style-type: none"> Absent or markedly decreased megakaryocytes Normal erythroid and myeloid maturation 	<p>Often progresses to pancytopenia and leukemic transformation</p>	<ul style="list-style-type: none"> Platelet transfusions Bone marrow transplantation
Wiskott-Aldrich syndrome	X-linked recessive disorder	Abnormal gene on proximal arm of X chromosome encodes regulatory protein of lymphocyte and platelet function.	<ul style="list-style-type: none"> Atopic dermatitis Thrombocytopenic purpura Increased susceptibility to infections 	<ul style="list-style-type: none"> Small (3 to 5 fL) defective platelets Normal-appearing megakaryocytes 	<p>Survival beyond teens rare. Infections or bleeding are major causes of death. 12% incidence of fatal malignancy.</p>	<p>Splenectomy may improve platelet count but often complicated by overwhelming sepsis/death</p>
Giant platelet disorders	Autosomal recessive	Dysfunction/absence of platelet receptor for von Willebrand factor (GP Ib-IX-V)	<ul style="list-style-type: none"> Easy bruising and severe hemorrhage with trauma/surgery 	<ul style="list-style-type: none"> Macrothrombocytopenia, severe platelet dysfunction 	<p>Bleeding tendency lifelong</p>	<p>For both Bernard-Soulier, MYH9RD: Desmopressin acetate may shorten bleeding time. Platelet transfusions for surgery/severe bleeding. Bernard-Soulier patients may develop antiplatelet antibodies because of GP Ib-IX-V on transfused platelets.</p>
<ul style="list-style-type: none"> MYH9-related disease (MYH9RD) 	Autosomal dominant	Nonmuscle myosin heavy chain gene (MYH9) mutations	<ul style="list-style-type: none"> Bleeding, nephritis, hearing loss, cataracts. Epstein, Fechtner, Sebastian syndrome or May-Hegglin anomaly previously diagnosed based on specific clinical findings at presentation but now regarded as one disorder. 	<ul style="list-style-type: none"> Macrothrombocytopenia, leukocyte inclusions, hematuria, proteinuria 	<p>Progressive high-frequency sensorineural hearing loss, glomerulonephritis and cataracts may develop anytime between infancy and adulthood.</p>	

superficial ecchymoses. Patients who have thrombocytopenia may also have persistent, profuse bleeding from superficial cuts. Petechiae, the pinhead-sized, red, flat, discrete lesions caused by extravasation of red cells from skin capillaries and often occurring in crops in dependent areas, are highly characteristic of decreased platelet number or function. Petechiae are nontender and do not blanch under pressure. They are asymptomatic and not palpable and should be distinguished from small telangiectasias and vasculitic (palpable) purpura. Purpura describes purplish discolorations of the skin due to the presence of confluent petechiae. Ecchymoses are nontender areas of bleeding into the skin that are typically small, multiple, and superficial and can develop without noticeable trauma. Ecchymoses often have a variety of colors due to the presence of extravasated blood (red or purple) and the ongoing breakdown of heme pigment in the extravasated blood by skin macrophages (green, yellow, or brown).

This pattern of bleeding differs from that of patients who have disorders of coagulation factors, such as hemophilia. Patients who have thrombocytopenia tend to have less deep bleeding into muscles or joints, more bleeding after minor cuts, less delayed bleeding, and less postsurgical bleeding. In addition, patients who have coagulation factor disorders tend not to have petechiae. Although rare, bleeding into the central nervous system is the most common cause of death due to thrombocytopenia. When such bleeding occurs, it is often preceded by a history of head trauma.

Evaluation

A thorough history and physical examination and judicious use of laboratory testing can lead to the appropriate diagnosis in most patients (Fig. 2). Patients should be questioned about past and current bleeding symptoms, including bruising with little or no trauma, nosebleeds, blood in the urine or stool, gum bleeding, bleeding with surgical or dental procedures, or excessive menstrual bleeding. Duration and onset of the bleeding symptoms may help determine whether the cause is acquired or congenital. If thrombocytopenia is due to an acquired cause, the onset of symptoms may be linked to a specific trigger (eg, infection). Congenital thrombocytopenia should be considered in patients who have a prolonged history of asymptomatic abnormal platelet counts or a family history of thrombocytopenia.

In children who have suspected or known thrombocytopenia, the skin, gingivae, and oral cavity should be examined carefully for evidence of bleeding. In hospitalized patients, careful examination for bleeding should be

performed at the site of indwelling catheters, drains, and incisions or areas of previous trauma. Table 4 lists the “red flags” in the history and physical examination of children who have thrombocytopenia that should lead to consideration of diagnoses other than ITP.

Laboratory Evaluation

The laboratory evaluation of thrombocytopenia begins with a CBC and evaluation of the PBS. Although a dying skill for most general practitioners, the ability to assess the PBS accurately is invaluable in the evaluation of children who have thrombocytopenia or other hematologic abnormalities. Consultation with a hematopathologist or experienced laboratory technologist may be useful.

The CBC should be examined closely for the platelet count and mean platelet volume (MPV) as well as for evidence of any other cytopenias (anemia or leukopenia). A platelet count that does not make sense clinically should be confirmed before undertaking extensive evaluation to be sure that thrombocytopenia exists and the finding is not due to artifact or laboratory error. Spurious thrombocytopenia can be caused by improper collection or inadequate anticoagulation of the blood sample, resulting in platelet clumps that are counted as leukocytes by automated cell counters. Once thrombocytopenia has been confirmed, an MPV that is significantly higher than normal suggests one of the macrothrombocytopenia syndromes. A mildly elevated MPV is consistent with a destructive cause. A low MPV is typically seen in patients who have Wiscott-Aldrich syndrome (WAS) gene mutations.

The PBS should be examined to estimate the platelet number (1 platelet/high power field=platelet count of $\sim 10 \times 10^3/\mu\text{L}$ [$10 \times 10^9/\text{L}$]), determine the platelet morphology and the presence or absence of platelet clumping, and assess whether there are associated white and red blood cell changes. Large platelets suggest either an ongoing platelet destructive process leading to the production of younger and larger platelets or the presence of a congenital macrothrombocytopenia syndrome. Small platelets in the appropriate clinical setting suggest WAS. The presence of schistocytes suggests a microangiopathic process such as DIC, HUS, or TTP. Spherocytes suggest autoimmune hemolytic anemia coupled with immune-mediated thrombocytopenia (Evans syndrome).

Other tests may be useful in determining the cause of the thrombocytopenia but are generally performed based on suggestive findings from the initial history and physical examination and laboratory testing. A positive direct

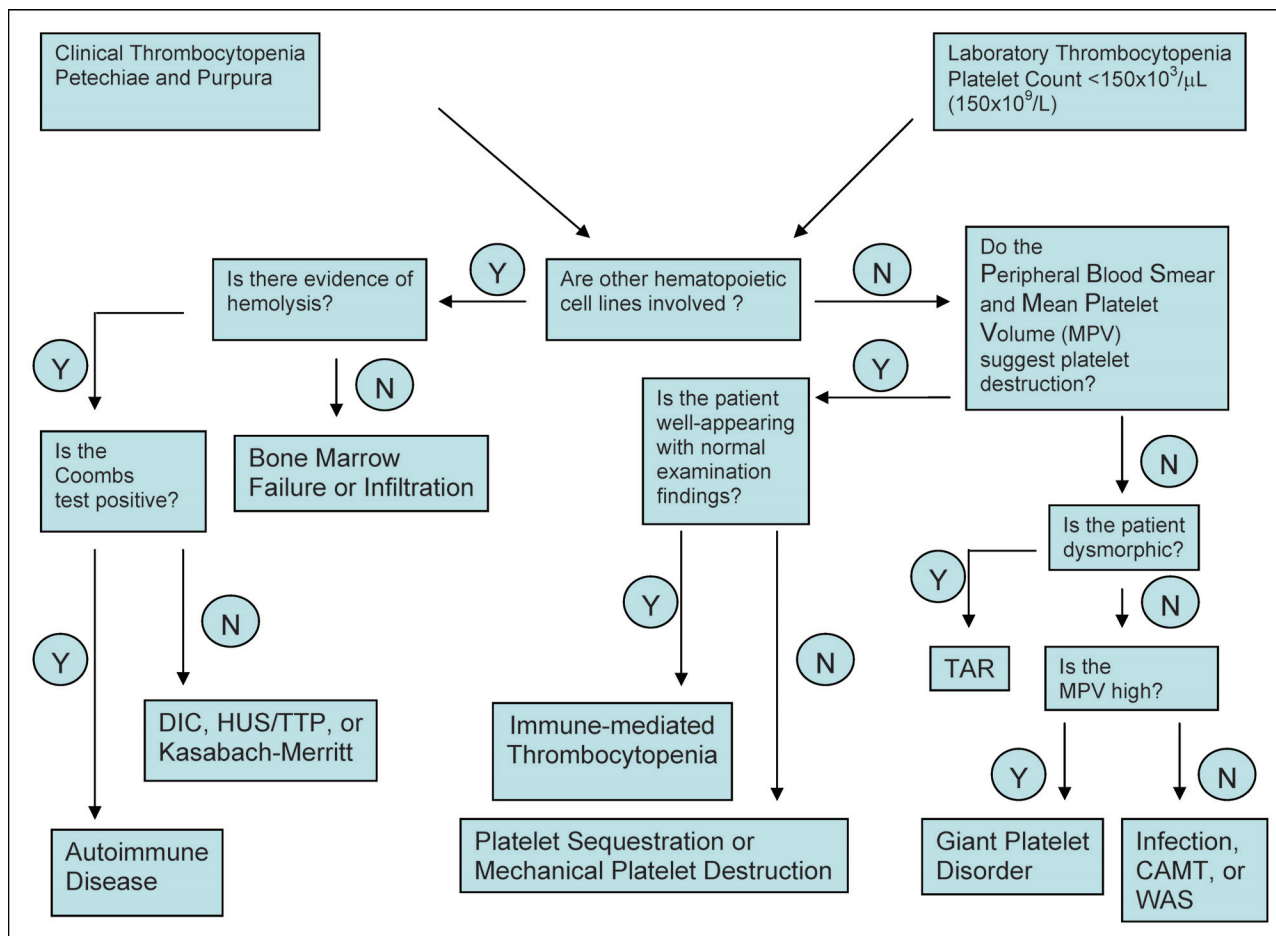


Figure 2. Diagnostic algorithm for thrombocytopenia. CAMT=congenital amegakaryocytic thrombocytopenia, DIC=disseminated intravascular coagulation, HUS=hemolytic-uremic syndrome, TAR=thrombocytopenia with absent radii syndrome, TTP=thrombotic thrombocytopenic purpura, WAS=Wiscott-Aldrich syndrome.

Coombs test suggests an autoimmune process in a patient who has evidence of hemolysis as well as spherocytes on the PBS. For patients who have persistent or chronic ITP, antinuclear antibody, serum immunoglobulins (IgG, IgA, IgM), and antiphospholipid antibodies should be considered. Fibrin degradation products and fibrinogen measurements are useful to diagnose intravascular coagulation.

If the PBS results are consistent with a microangiopathic process, additional tests should be considered, including serum lactate dehydrogenase and creatinine to assess for HUS or TTP. HIV testing should be considered because thrombocytopenia may be the initial disease manifestation in as many as 10% of patients who have HIV infection. If clinical suspicion or local prevalence is high, tests to identify hepatitis C viral infection or *Helicobacter pylori* infection should also be considered.

Screening tests for inherited disorders associated with thrombocytopenia should be considered in patients who experience chronic thrombocytopenia, especially in the presence of short stature or other congenital anomalies.

Platelet antibodies can be detected by a variety of assays. Although many of these assays have high sensitivity, they lack specificity and are not indicated or performed routinely to confirm the diagnosis of acute ITP in children.

A bone marrow examination is not necessary in most cases of isolated unexplained thrombocytopenia in children. In general, a bone marrow examination is indicated when clinical signs or symptoms suggest either marrow infiltration or failure. These findings include pancytopenia; the presence of blasts on the PBS; and the presence of systemic symptoms such as fever, fatigue, weight loss, or bone pain. A bone marrow examination also is indi-

cated for unexplained, chronic, stable thrombocytopenia, even when the presumed diagnosis is ITP, or if the subsequent clinical course is inconsistent with the natural history of ITP because of the development of new clinical signs or symptoms or laboratory abnormalities.

Treatment

Management of thrombocytopenia in an individual patient should be guided by an understanding of its cause and predicted clinical course. Correction of the cause may not be possible (eg, congenital thrombocytopenias) or may not be necessary (eg, mild-to-moderate ITP). The principal management goal in all patients who have thrombocytopenia is to maintain a safe platelet count to prevent significant bleeding, not to achieve a normal platelet count. What constitutes a safe platelet count in a particular patient varies, depending on the cause of the thrombocytopenia and consideration of all other aspects of hemostasis. For patients who have significant bleeding symptoms, treatment is essential. Asymptomatic or minimally symptomatic thrombocytopenia may be treated if the thrombocytopenia is severe or the perceived risk of bleeding is great.

Activity Restrictions

When moderate-to-severe thrombocytopenia is recognized, implementing reasonable precautions to minimize bleeding risk is recommended. These steps include trauma precautions (eg, avoidance of contact sports and use of a helmet while cycling) and avoidance of medications that have antiplatelet or anticoagulant activity (including aspirin-containing preparations, ibuprofen, and other nonsteroidal anti-inflammatory drugs).

Invasive Procedures

A platelet count greater than $50 \times 10^3 / \mu\text{L}$ ($50 \times 10^9 / \text{L}$) provides safety for most invasive procedures. If the risks of potentially serious bleeding are believed to be severe, a platelet count of greater than $100 \times 10^3 / \mu\text{L}$ ($100 \times 10^9 / \text{L}$) is often required by surgeons or anesthesiologists. For common minor procedures, such as tooth extractions, a platelet count of 30 to $50 \times 10^3 / \mu\text{L}$ ($50 \times 10^9 / \text{L}$) often is sufficient. (1) For patients who have lower platelet counts, some measure to increase the platelet count immediately before the procedure may be required. A short course of corticosteroids (prednisone 2 mg/kg per day for 1 week) or a single dose of immune globulin intravenous (IGIV) (1 g/kg) is often sufficient to increase the platelet count acutely for procedural hemostasis. Platelet transfusions can be used in urgent situations. Although platelet survival in the circulation of

Table 4. Red Flags Suggesting a Diagnosis Other Than Immune Thrombocytopenic Purpura

History

- Fever
- Bone pain
- Weight loss
- Fatigue
- Recent history of infections or vaccinations
- Past medical history of diseases associated with thrombocytopenia (eg, autoimmune disorders, cirrhosis)
- Dietary history suggestive of iron, vitamin B12, or folate deficiency
- Exposure to medications known to be associated with thrombocytopenia
- Travel history to an endemic area for malaria

Physical Examination

- Lymphadenopathy
- Splenomegaly
- Joint swelling
- Short stature
- Limb defects, including radial agenesis and thumb abnormalities
- Cataracts
- Sensorineural hearing loss
- Oral leukoplakia
- Dystrophic nails
- Eczema in male patient
- Frequent infections
- Superficial hemangiomas

patients who have destructive thrombocytopenias may not be normal, platelet transfusion nearly always provides prompt, satisfactory hemostasis, even if only for a short duration.

Emergency Management of Critical Bleeding

Patients who have severe thrombocytopenia and critical bleeding require immediate transfusion of platelets regardless of the cause of the thrombocytopenia. ICH is the most serious consequence of severe thrombocytopenia. Early diagnostic imaging should be considered for patients who have severe thrombocytopenia and neurologic signs or symptoms to identify ICH. For patients who have unstable or progressive ICH, emergency craniotomy may be necessary. For patients who have ITP with life-threatening bleeding, in addition to platelets, adjunctive treatment with high doses of corticosteroid (intravenous methylprednisolone 30 mg/kg

Table 5. Initial Treatment for Newly Diagnosed Immune Thrombocytopenic Purpura (ITP) With Significant Bleeding or Risk of Bleeding

Treatment	Mechanism of Action	Response Rate	Toxicities	Comments
<p>Corticosteroids</p> <p>Dosing varies from prednisone 2 mg/kg per day orally for 2 to 4 weeks to high-dose methylprednisolone 30 mg/kg per day (maximum, 1 g) intravenously for 3 to 7 days</p>	<ul style="list-style-type: none"> Reduces antibody production Reduces reticuloendothelial system phagocytosis of antibody-coated platelets Improves vascular integrity Improves platelet production 	<p>Up to 75% achieve platelet response, depending on dose; response to therapy usually within 2 to 7 days</p>	<ul style="list-style-type: none"> Behavioral changes Sleep disturbance Increased appetite Weight gain Gastritis/gastrointestinal hemorrhage Immunosuppression Poor linear growth Nausea/vomiting Severe headache Fever Chills More pronounced in older patients 	<ul style="list-style-type: none"> No curative benefit known Often, a drop in platelet count after steroids discontinued Repeated courses may be necessary if significant bleeding symptoms persist or recur No curative benefit known 30% have significant drop in platelet count in 2 to 6 weeks IGIV appears to improve platelet counts more reliably than corticosteroids or no treatment. Some experts believe that in patients who fail to show any platelet rise with IGIV, the diagnosis of ITP should be reconsidered and bone marrow assessment strongly considered
<p>Immune Globulin Intravenous (IGIV)</p> <p>Single dose 1 g/kg</p>	<p>Unknown and likely multifactorial. Theories include:</p> <ul style="list-style-type: none"> Reticuloendothelial system blockade/inhibition Autoantibody neutralization by anti-idiotypic antibodies Increased autoantibody clearance due to competitive inhibition of immunoglobulin Fc receptor 	<p>>80% achieve platelet response; response to therapy usually within 24 hours</p>	<ul style="list-style-type: none"> Hemolysis (can be severe) Disseminated intravascular coagulation Renal failure (rare) Headache, fever, chills less common than with IGIV 	<ul style="list-style-type: none"> With higher doses, is comparable to IGIV Only effective in children who are Rho(D)-positive. Should only be given if hemoglobin >10 g/dL (100 g/L) and Coombs-negative. Treated patients must be watched for presence and sequelae of significant hemolysis. IGIV is generally preferred.
<p>Anti-Rho(D) immune globulin</p> <p>Single dose 50 to 75 μg/kg</p>	<p>Specific red blood cell antibodies coat red blood cells, which are then taken up by the reticuloendothelial system in place of antibody-coated platelets</p>	<p>50% to 77% achieve platelet response, depending on dose; up to 50% respond within 24 hours</p>	<ul style="list-style-type: none"> Hemolysis (can be severe) Disseminated intravascular coagulation Renal failure (rare) Headache, fever, chills less common than with IGIV 	<ul style="list-style-type: none"> With higher doses, is comparable to IGIV Only effective in children who are Rho(D)-positive. Should only be given if hemoglobin >10 g/dL (100 g/L) and Coombs-negative. Treated patients must be watched for presence and sequelae of significant hemolysis. IGIV is generally preferred.

Table 6. Treatment Options for Children Who Have Refractory Immune Thrombocytopenic Purpura With Significant Bleeding Symptoms

Treatment	Mechanism of Action	Response Rate	Toxicities	Comments
Splenectomy	Reduces destruction of both autologous and transfused platelets	Usually raises the platelet count within hours; 60% to 70% achieve a permanent remission	<ul style="list-style-type: none"> • Intraoperative bleeding • Life-threatening infections 	Even those not demonstrating rise in platelet count may be more responsive to previously failed medical therapies.
High-dose methylprednisolone 30 mg/kg per day (maximum, 1 g) for 3 days followed by 20 mg/kg per day for 4 days	<ul style="list-style-type: none"> • Reduces antibody production • Reduces reticuloendothelial system phagocytosis of antibody-coated platelets • Improves vascular integrity • Improves platelet production 	<ul style="list-style-type: none"> • >60% to 100% achieve platelet response; • response to therapy usually within 2 to 7 days 	<ul style="list-style-type: none"> • Behavioral changes • Increased appetite • Gastritis/gastrointestinal hemorrhage • Immunosuppression • Poor linear growth • Decreased bone mineralization 	If repeated courses necessary, alternative therapies should be considered.
Single or combination regimens: cyclosporin A, azathioprine, vincristine, cyclophosphamide, danazol ± prednisone, immune globulin intravenous (IGIV)	Immunosuppression via cytotoxic effects	~70% achieve platelet response; response to therapy varies but generally days to months	<ul style="list-style-type: none"> • Usually well tolerated with manageable infusion-related adverse effects. 	Experience in children limited.
Rituximab 375 mg/m ² per dose intravenously weekly for 4 weeks	Not completely defined. Possibly, source of pathogenic antibodies (B lymphocytes) removed by selective destruction of CD20-positive cells, resulting in decreased antibody production.	At least 30% complete response rate lasting an average of 13 months; response is usually prompt (1 to 2 weeks) but may take up to 8 weeks. Delay may be result of time needed to clear circulating pathogenic antibodies.	<ul style="list-style-type: none"> • Hypogammaglobulinemia is infrequent. IGIV 400 mg/kg every 3 to 4 weeks may be administered to maintain normal concentrations. • Progressive multifocal leukoencephalopathy has been reported, but causal relationship not confirmed. 	If thrombocytopenia recurs, second course appears to be safe and effective.
Thrombopoietin receptor agonists Romiplostim 1 to 10 µg/kg subcutaneously weekly Eltrombopag 25 to 75 mg orally daily	Romiplostim, a subcutaneous thrombopoiesis-stimulating Fc peptide fusion protein, and eltrombopag, an orally active, nonpeptide thrombopoietin receptor agonist, act by stimulating platelet production.	As high as 80% in adult patients. Studies in children extremely limited. Use currently restricted to refractory patients who have significant bleeding symptoms.	<ul style="list-style-type: none"> • Thrombosis • Increased concentrations of bone marrow reticulin 	No effect on underlying pathologic mechanism, and rebound thrombocytopenia when drugs are stopped is common. Used to keep platelets in safe range (50 to 200 × 10 ³ /µL [50 to 200 × 10 ⁹ /L]). Very expensive, and long-term experience limited.

up to 1 g/day for 3 days) and a single dose of IGIV (1 g/kg) is also appropriate. Emergency splenectomy may be considered in cases of refractory ITP accompanied by life-threatening hemorrhage.

Thrombocytopenia Associated With Other Cytopenias

Patients who have pancytopenia with systemic symptoms or significant findings on examination should be evaluated carefully in a timely manner because they are at increased risk for a serious disorder that may require urgent intervention. Consultation with a pediatric hematologist should be strongly considered. Treatment of the identified underlying primary disorder guides subsequent management. For such patients, maintenance of a safe platelet count may be only a small part of the overall treatment plan.

Isolated Thrombocytopenia

The most likely diagnosis in an otherwise healthy child who has isolated thrombocytopenia is ITP. Most patients do not have serious bleeding (including those whose platelet counts are $<10 \times 10^3/\mu\text{L}$ [$10 \times 10^9/\text{L}$]). ICH is extremely rare, with an incidence of 0.1% to 0.5%. Although treatments for childhood ITP may reduce the severity and duration of the initial thrombocytopenic episode and presumably the risk of bleeding, they do not appear to affect the eventual recovery rate. Up to two thirds of children who have ITP recover within 6 months of presentation with or without treatment. (3)(5)

Most experts agree that pharmacologic intervention is not generally needed for children who have mild-to-moderate thrombocytopenia (platelet counts $>30 \times 10^3/\mu\text{L}$ [$30 \times 10^9/\text{L}$]) because they are unlikely to have serious bleeding. Exceptions to this policy include children who have concomitant or preexisting conditions that increase their risk for severe bleeding and children undergoing procedures likely to include blood loss. (6)

For patients whose platelet counts are less than $30 \times 10^3/\mu\text{L}$ ($30 \times 10^9/\text{L}$), treatment recommendations are based on the presence and severity of associated bleeding or the risk thereof. Although there is no defined means to predict which children who have ITP will suffer from an ICH, retinal hemorrhages and extensive mucosal bleeding or “wet purpura” have been reported to precede and possibly predict spontaneous ICH. (4) Thus, any individual who has ITP and actual or obvious potential for significant bleeding requires immediate treatment, regardless of the platelet count.

When therapy is indicated, the primary treatment options for the newly diagnosed patient are corticoste-

roids, IGIV, and anti-Rho(D) immune globulin (Table 5). Several studies have shown that the duration of symptomatic thrombocytopenia is shortened by any of these three interventions compared with no treatment. All ITP therapies are temporizing interventions intended for rapid reversal of a real or perceived risk for significant hemorrhage. They do not need to be continued until normal platelet counts are reached. Therapy is targeted to increase the platelet count above a threshold (usually $>20 \times 10^3/\mu\text{L}$ [$20 \times 10^9/\text{L}$]) that stops bleeding or eliminates the risk of serious bleeding. (6) Platelet transfusions are indicated in patients who have ITP only in the setting of life-threatening bleeding, such as ICH. Because of accelerated platelet destruction in ITP, platelet transfusions result in a relatively limited rise in the platelet count of very short duration (measured in hours or even minutes) that may be adequate for the immediate hemostasis required in the setting of ICH but otherwise is of no benefit.

Almost all children who develop ITP are treated in the ambulatory setting. Patients who require pharmacologic intervention with IGIV or high-dose intravenous corticosteroids are usually hospitalized for an average of 1 to 3 days. Platelet counts are monitored once or twice weekly, depending on the clinical situation and severity of the thrombocytopenia. When recovery of platelet counts is detected, the interval between platelet count assessment may be lengthened. Monitoring should continue until the platelet count has returned to normal and is stable.

Approximately 20% to 30% of children who present with ITP eventually develop chronic ITP, defined as persistent thrombocytopenia beyond 12 months from the time of presentation. Patients who have chronic ITP are usually clinically indistinguishable from those who have acute ITP at presentation. Children younger than 10 years of age are more likely to have remissions than older patients. Children whose bleeding manifestations last more than 14 days are substantially more likely to develop chronic ITP.

All children who have persistent (3 to 12 months) or chronic (>12 months) ITP should have their cases reviewed and managed by a pediatric hematologist. Individuals who have chronic ITP should undergo evaluation that includes bone marrow examination to exclude other causes of thrombocytopenia. In chronic ITP, platelet counts tend to range between 20 and $75 \times 10^3/\mu\text{L}$ (20 and $75 \times 10^9/\text{L}$); consequently, many patients require no or only intermittent treatment for episodes of significant bleeding or increased risk of bleeding.

A small percentage of pediatric patients who have ITP

Summary

- Thrombocytopenia should be suspected in any child presenting with a history of easy bruising or bleeding or petechiae, but it also may present as an incidental finding in an asymptomatic individual.
- Thrombocytopenia may be caused by either increased destruction or removal of platelets from the circulation or decreased production of platelets.
- Destructive mechanisms resulting in thrombocytopenia include immune-mediated destruction, platelet activation and consumption, mechanical platelet destruction, and platelet sequestration or trapping.
- Impaired platelet production may be due to bone marrow infiltration, suppression, or failure or defects in megakaryocyte development and differentiation.
- A thorough history and physical examination and judicious use of laboratory testing can lead to the appropriate diagnosis in most patients who have thrombocytopenia.
- Childhood ITP generally presents with the sudden appearance of bruising, bleeding, or petechiae in an otherwise healthy child.
- The diagnosis of ITP can be made using two criteria: 1) isolated thrombocytopenia with otherwise normal blood counts and peripheral blood smear and 2) no clinically apparent associated conditions that may cause thrombocytopenia.
- Further evaluation, including bone marrow assessment, should be considered in patients who have atypical clinical or laboratory features at presentation; thrombocytopenia lasting more than 6 months; or a subsequent clinical course that is inconsistent with the natural history of ITP, including failure to respond to usually effective therapies.
- Management of thrombocytopenia should be guided by an understanding of its cause and clinical course, with the principal goal in all patients being to maintain a safe platelet count to prevent significant bleeding.
- For childhood ITP, pharmacologic intervention, including corticosteroids, IGIV, and anti-Rho(D) immune globulin, has been shown to raise the platelet count more quickly than no therapy and is recommended for children who have or at risk for severe or life-threatening bleeding, based on strong evidence.
- ITP in children usually is short-lived, with at least two thirds of patients making a full and sustained recovery within 6 months of presentation, with or without treatment.

and significant hemorrhagic symptoms demonstrate resistance to both corticosteroids and IGIV. Management of such so-called refractory ITP is difficult (Table 6).

Pulse intermittent high-dose corticosteroids and splenectomy have been the mainstays of treatment in these situations, although not without significant risks. Newer treatment modalities that may be useful include rituximab, a chimeric anti-CD20 monoclonal antibody, and the thrombopoietin receptor agonists romiplostim and eltrombopag, although studies of these agents in children are limited (9)(10)(11) and not approved by the United States Food and Drug Administration for children younger than 18 years. The recent use of thrombopoietin receptor agonists reflects a new paradigm in the treatment of ITP, with the focus not on reducing platelet consumption through immune modulation or suppression but on increasing platelet production.

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PIR Quiz

Quiz also available online at <http://pedsinreview.aappublications.org>.

1. A 4-year-old boy is brought to the office with a 3-week history of bruising. He has had no other complaints. He has mild bruising but no petechiae and no mucosal bleeding. His physical examination findings are otherwise normal. Laboratory results include a white blood cell count of $8.4 \times 10^3/\mu\text{L}$ ($8.4 \times 10^9/\text{L}$), hemoglobin of 13.4 g/dL (134 g/L), and platelet count of $31 \times 10^3/\mu\text{L}$ ($31 \times 10^9/\text{L}$). The *most* appropriate management is:
 - A. High-dose intravenous corticosteroids.
 - B. Intravenous anti-D.
 - C. Intravenous gamma globulin.
 - D. Observation.
 - E. Oral corticosteroids.
2. A 4-year-old girl presents with a 5-week history of bruising but is otherwise well. On physical examination, the only abnormal finding is increased bruising and scattered petechiae. Her platelet count is $29 \times 10^3/\mu\text{L}$ ($29 \times 10^9/\text{L}$), hemoglobin is 9.5 g/dL (95 g/L), and white blood cell count is $2.1 \times 10^3/\mu\text{L}$ ($2.1 \times 10^9/\text{L}$). The *most* appropriate next step is to:
 - A. Administer antibiotics.
 - B. Observe the child.
 - C. Obtain antiplatelet antibodies.
 - D. Obtain Epstein-Barr virus titers.
 - E. Perform a bone marrow aspiration.
3. An 18-month-old girl has a blood count performed at a health supervision visit. The child is well and her physical examination findings are normal. The laboratory calls because the platelet count is $1 \times 10^3/\mu\text{L}$ ($1 \times 10^9/\text{L}$). The hemoglobin is 13.5 g/dL (135 g/L), white blood cell count is $7.6 \times 10^3/\mu\text{L}$ ($7.6 \times 10^9/\text{L}$), and absolute neutrophil count is $3.9 \times 10^3/\mu\text{L}$ ($3.9 \times 10^9/\text{L}$). The *most* appropriate next step is to:
 - A. Measure immunoglobulins, antinuclear antibody, and antiphospholipid antibodies.
 - B. Measure prothrombin and partial thromboplastin times.
 - C. Perform a bone marrow aspiration.
 - D. Refer to a pediatric hematologist.
 - E. Repeat the platelet count.
4. A 6-year-old boy who has known chronic immune thrombocytopenic purpura is involved in a motor vehicle accident and arrives in the emergency department unresponsive. Emergency computed tomography scan of the head reveals a large subdural hematoma. The child's blood type is A-negative. The platelet count is $1 \times 10^3/\mu\text{L}$ ($1 \times 10^9/\text{L}$). You administer a platelet transfusion and high doses of intravenous methylprednisolone and begin intravenous gamma globulin. During the emergency craniotomy, it is difficult to control the bleeding. The *most* appropriate next therapy is:
 - A. Anti-D immune globulin.
 - B. Cyclophosphamide.
 - C. Emergency splenectomy.
 - D. Plasmapheresis.
 - E. Rituximab (anti-CD 20 monoclonal antibody).

5. A 7-year-old girl presents with a 3-day history of bruising and an episode of epistaxis lasting 30 minutes. On physical examination, the only abnormalities are scleral icterus, widespread bruising, and cutaneous as well as mucosal petechiae. Laboratory results include a platelet count of $3 \times 10^3/\mu\text{L}$ ($3 \times 10^9/\text{L}$), hemoglobin of 7.8 g/dL (78 g/L), white blood cell count of $12.9 \times 10^3/\mu\text{L}$ ($12.9 \times 10^9/\text{L}$), absolute neutrophil count of $8.8 \times 10^3/\mu\text{L}$ ($8.8 \times 10^9/\text{L}$), and mean corpuscular volume of 86 fL. Urinalysis is negative for red blood cells. The *most* appropriate next study is:
- A. Antiplatelet antibodies.
 - B. Bone marrow aspirate.
 - C. Direct antiglobulin (Coombs) test.
 - D. Flow cytometry on peripheral blood.
 - E. Serum blood urea nitrogen and creatinine assessment.

Corrections

The caption for Figure 2 in the article entitled “Focus on Diagnosis: Urine Electrolytes” in the February issue of the journal (*Pediatr Rev.* 2011;32:65–68) is incorrect. The correct caption should read, “A graphic illustration of a positive urine anion gap, with the number of unmeasured anions exceeding the number of unmeasured cations. When this situation occurs in the context of metabolic acidosis, it is consistent with renal tubular acidosis, indicating an impaired ability to excrete protons in the urine as ammonium.” We regret the error.

The caption for Figure 1 in the article entitled “Sacral Dimples” in the March issue of the journal (*Pediatr Rev.* 2011;32:109–114) is incorrect. The correct caption should read, “Solitary dimple whose location is greater than 2.5 cm above the anus indicated the need for further evaluation. . . .” We regret the error.

Thrombocytopenia in Infants and Children

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