Thrombocytopenia During Childhood: What the Pediatrician Needs to Know

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

1. Describe the number, function, and life span of platelets.
2. Define the mechanisms of thrombocytopenia and the relative bleeding risk at any given platelet count.
3. Provide a differential diagnosis of neonatal thrombocytopenia and describe the clinical presentation and management of the most common forms.
4. Describe the usual presentation and laboratory tests in the child who has acute idiopathic thrombocytopenic purpura, review the treatments, and know the usual prognosis.
5. List the differential diagnosis of children who have chronic thrombocytopenia and methods of differentiating the various causes.

Introduction and Case History

Thrombocytopenia is defined as a platelet count less than $150 \times 10^3/\text{mcL}$ ($150 \times 10^9/\text{L}$), irrespective of the patient's age. Thrombocytopenia is encountered commonly by pediatricians. Therefore, a review of the pathophysiology, differential diagnosis, and management of thrombocytopenia is in order.

A 4-year-old boy who is recovering from a minor respiratory infection suddenly develops petechiae and bruises on his trunk and extremities. Two days later, after a transient nosebleed, he is brought to his physician's office. His past medical history and family history are unremarkable. Findings on his physical examination are normal except for scattered crops of petechiae and multiple bruises. There is no active bleeding from the nose or other sites. A complete blood count (CBC) shows a hemoglobin of 12.7 g/dL (127 g/L), a white blood cell (WBC) count of $8 \times 10^3/\text{mcL}$ ($8 \times 10^9/\text{L}$), a normal differential count, and platelet count of $6 \times 10^3/\text{mcL}$ ($6 \times 10^9/\text{L}$). The diagnosis of idiopathic thrombocytopenic purpura (ITP) is suspected.

Abbreviations

ALPS:	autoimmune lymphoproliferative syndrome
CBC:	complete blood count
DIC:	disseminated intravascular coagulation
HPA:	human platelet antigen
ICH:	intracranial hemorrhage
ITP:	idiopathic thrombocytopenic purpura
IVIG:	intravenous immune globulin
MCV:	mean corpuscular volume
MPV:	mean platelet volume
NAIT:	neonatal alloimmune thrombocytopenia
PT:	prothombin time
PTT:	partial thromboplastin time
TTP:	thrombotic thrombocytopenic purpura
WBC:	white blood cell

Platelet Number and Function in Health and Disease

Platelets are tiny acellular fragments produced in the bone marrow by polyploid cells called megakaryocytes. Platelets are about one fifth the diameter of erythrocytes, and their volume is 7 to 9 fL. They survive in the body for 9 to 10 days. Their major function is to promote primary hemostasis by forming small aggregates or plugs in the microcirculation. Platelets contain membrane receptors that enhance both adhesion (platelets sticking to a damaged blood vessel wall) and aggregation (platelets sticking to one another). The former is mediated by von Willebrand factor, a large adhesive glycoprotein, and the latter is enhanced by fibrinogen. Platelets are metabolically active, functioning essentially as small circulating secretory glands.

A hemorrhagic tendency results when the platelets are deficient in number (thrombocytopenia) or functionally defective. This review deals with the former. When the platelet

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Table 1. Clinical Manifestations of Platelet Disorders

- Petechiae
- Purpura
- Gingival bleeding
- Epistaxis
- Menorrhagia
- Gastrointestinal bleeding
- Hematuria
- Central nervous system hemorrhage

Table 2. Mechanisms of Thrombocytopenia

Diminished Platelet Production

- Marrow infiltration
- Marrow injury
- Ineffective thrombopoiesis

Shortened Platelet Life Span

- Immune (antibody or immune complex)
  —Idiopathic thrombocytopenic purpura
  —Neonatal alloimmune thrombocytopenia
  —Infection
  —Heparin
- Nonimmune (mechanical)
  —Disseminated intravascular coagulation
  —Hemolytic–uremic syndrome
  —Thrombotic thrombocytopenic purpura
  —Infection

Platelet Sequestration or Pooling (Hypersplenism)

Platelet Loss or Dilution

count is reduced, primary hemostasis is impaired, and mucocutaneous bleeding ensues. The clinical manifestations include petechiae (singly or in crops, often at pressure points or other sites of trauma), superficial bruises or purpura, and hemorrhage from mucosal surfaces, most commonly the nose and mouth (Table 1). For children who have thrombocytopenia, clinically significant hemorrhage in internal organs is rare.

Bruises seen in children who have thrombocytopenia are on the arms and trunk as well as the legs; bruises seen in normal active children typically are over the pretibial surfaces. Generalized bruises also are encountered in children who are victims of child abuse, but they do not have petechiae or thrombocytopenia. Children who have various forms of vasculitis also may have large bruises (as well as petechial lesions), usually accompanied by a normal or increased platelet count. Large soft-tissue hematomas, as well as joint and muscle hemorrhage, are characteristic of hemophilia and other blood coagulation disorders but are uncommon in patients who have thrombocytopenia.

The pathophysiologic mechanisms of thrombocytopenia are outlined in Table 2. Platelet number can be reduced as a consequence of decreased production, increased destruction, sequestration, or loss. The body has "reserve capacity" with regard to platelets. Although the normal platelet count is 150 to 450×10^3/mcL (150 to 450×10^9/L), primary hemostasis is not impaired until the platelet count is below 75×10^3/mcL (75×10^9/L). Spontaneous bleeding does not occur unless the platelet count is less than 50×10^3/mcL (50×10^9/L), and noticeable or clinically significant hemorrhage rarely occurs unless the platelet count declines to less than 20×10^3/mcL (20×10^9/L). Most patients who have life-threatening hemorrhage due to thrombocytopenia have platelet counts less than 10×10^3/mcL (10×10^9/L). At any given platelet count, platelet function or associated anatomic or blood coagulation defects affect the bleed-

ing tendency. Table 3 summarizes the relationship between platelet count and bleeding risk.

General Principles of Evaluation and Management

Mild thrombocytopenia may not result in bleeding, but it can be the initial manifestation of serious disease. The most important parts of the evaluation are the medical history and the physical examination. These allow for assessment of hemorrhage and evaluation for underlying disease. The CBC and peripheral blood film also provide

Table 3. Relationship Between Platelet Count and Bleeding

Platelet Count ($\times 10^3$/mcL [$\times 10^9$/L])	Signs and Symptoms
>100	None
50 to 100	Minimal (after major trauma and surgery)
20 to 50	Mild (cutaneous)
5 to 20	Moderate (cutaneous and mucosal)
<5	Severe (mucosal and central nervous system)

Other variables: function of platelets, anatomic defect, associated coagulopathy

invaluable information. Other diagnostic studies often are not required. However, on occasion, blood coagulation tests such as the prothrombin time (PT) and partial thromboplastin time (PTT) and the assessment of platelet function can be helpful. At one time, platelet function was assessed by the bleeding time, but this test has become outmoded. Use of a platelet function analyzer and platelet aggregation testing is sometimes of value. Assessment of platelet function in the laboratory is difficult in patients who have thrombocytopenia. A bone marrow aspirate sometimes is necessary to differentiate thrombocytopenia due to decreased production from that resulting from increased destruction. Analysis of the aspirate usually is indicated when neutropenia, anemia, or other evidence of a primary marrow disorder (eg, leukemia or aplastic anemia) is present. The differential diagnosis and methods of managing thrombocytopenia differ according to the child's age.

Neonatal Thrombocytopenia

Neonates who are well, even the smallest preterm infants, should have platelet counts in excess of 150×10^3/mcL (150×10^9/L). Thrombocytopenia in the newborn may manifest as generalized petechiae, ecchymosis, and mucous membrane (and rarely internal) bleeding. Whether the infant is basically "well" or "sick" should be determined initially.

Nonimmune Platelet Destruction

The most common setting for neonatal thrombocytopenia is a baby who is ill, often with infection or respiratory distress. Thrombocytopenia in this setting usually is due to destruction of platelets resulting from vasculitis, endotoxin, immune complexes, or disseminated intravascular coagulation (DIC). Decreased platelet production and pooling or sequestration in the spleen may be contributory. Virtually any infection can trigger thrombocytopenia, including intrauterine viral infection and perinatally acquired bacterial sepsis. The findings of low birthweight for gestational age, microcephaly, and other congenital abnormalities suggest the diagnosis of cytomegalovirus or another intrauterine viral infection. Thrombocytopenia also is a feature of necrotizing enterocolitis and respiratory distress syndrome. It also may be seen transiently in infants whose mothers had preeclampsia.

In addition to treating the underlying disorder, platelet transfusions are recommended when the platelet count is less than 10 to 20×10^3/mcL (10 to 20×10^9/L), when the baby is hemorrhaging from puncture sites or mucous membranes, or when an invasive procedure is planned. Administration of 10 to 15 mL/kg of a platelet concentrate often improves hemostasis by temporarily raising the platelet count.

Decreased Platelet Production

On occasion, thrombocytopenia due to decreased production is encountered in the neonate. The most striking of these disorders is the thrombocytopenia absent radii syndrome, in which megakaryocytes are absent in the bone marrow. Affected children are managed with platelet transfusions. Interestingly, they "recover" their megakaryocytes and often normalize their platelet counts by 2 or 3 years of age. Rarely, thrombocytopenia due to decreased production occurs in the setting of neonatal leukemia or aplastic anemia. Physical findings or other blood count abnormalities usually are apparent.

Immune Thrombocytopenia

In contrast to the thrombocytopenia seen in sick neonates who have infection, isolated thrombocytopenia (with an otherwise normal blood count) sometimes is encountered in "well" infants who are born at term and show no abnormalities on the physical examination other than bleeding manifestations. These babies usually have immune-mediated thrombocytopenia due to transplacental passage of an antiplatelet antibody from the mother.

As outlined in Table 4, immune thrombocytopenia in the newborn infant usually has one of two causes: an autoantibody affecting a mother who has ITP or an alloantibody directed against an antigen on the neonate's platelets that the mother lacks.

Infants whose mothers have ITP rarely exhibit serious hemorrhage despite transplacental passage of the antibody. In fact, many do not have thrombocytopenia at birth. Of note, the platelet count often declines below values seen in cord blood by the second to fourth postnatal day. For those occasional babies who exhibit marked cutaneous hemorrhage or mucosal bleeding, intravenous immune globulin (IVIG) is the treatment of choice. Corticosteroids and platelet transfusions have limited utility. Thrombocytopenia resolves after several months following catabolism of the passively acquired antibody. Other forms of immune-mediated thrombocytopenia in the neonate due to acquisition of maternal antiplatelet antibody against a drug or as a consequence of systemic lupus erythematosus are rare. ITP is not encountered in neonates due, in part, to their impaired immune responses.

Neonatal alloimmune thrombocytopenia (NAIT) is analogous to Rh hemolytic disease involving the red

Table 4. Immune Thrombocytopenia in the Neonate

	Maternal Idiopathic Thrombocytopenic Purpura	Neonatal Alloimmune Thrombocytopenia
Approximate frequency	1 in 50,000	1 in 2,000
Type of antibody	Maternal *auto*antibody	Maternal *allo*antibody
Target antigens	Common to all platelets	Antigen on neonate's platelets but not on mother's (usually HPA-1a)
Intrauterine hemorrhage	None	Can be serious (hydrocephalous or death resulting from intracranial hemorrhage)
Treatment of fetus	Unnecessary	IVIG or compatible platelet transfusion
Postnatal hemorrhage	Uncommon	Can be serious
Postnatal treatment	Usually unnecessary; IVIG if platelet count <10 to 20×10³/mcL (<10 to 20×10⁹/L)	Often required; maternal platelets or IVIG if platelet count <20 to 30×10³/mcL (<20 to 30×10⁹/L)
Resolution of neonatal thrombocytopenia	Within 2 to 3 months	Within several weeks
Recurrence rate in subsequent pregnancies	High	High

HPA=human platelet antigen, IVIG=intravenous immune globulin.

blood cell. The most common offending platelet antigen is the human platelet antigen (HPA)-1a antigen, present on the platelet surface of 98% of normal individuals. A small percentage of those 2% of women who are HPA-1a-negative (and whose partners are likely HPA-1a-positive) produce an anti-HPA-1a antibody that crosses the placenta and causes fetal thrombocytopenia during the second trimester. Because the antibody affects platelet function and induces thrombocytopenia, severe hemorrhage may ensue.

Intracranial bleeding resulting in fetal death or hydrocephalus may be encountered; bleeding at delivery also is a risk. Some evidence suggests that diagnosing NAIT in the fetus during the second trimester (by percutaneous umbilical venous sampling), followed by intrauterine platelet transfusions or administration of IVIG to the mother, can be lifesaving. This strategy generally is feasible, but only when NAIT is anticipated as a result of a history of a previously affected infant. More commonly, severe thrombocytopenia and accompanying hemorrhage in an otherwise healthy term infant leads to suspicion of the diagnosis. Platelet transfusion from a random donor usually is ineffective (because the donor is likely to be HPA-1a-positive). However, platelets derived from the mother (lacking the antigen) survive normally following transfusion. This differential response to platelet transfusions (ineffective from a random donor but effective when derived from the mother) represents the best readily available diagnostic test and also serves as treatment.

Platelet antigen and antibody testing are unavailable except in major referral centers. Therefore, the diagnosis of NAIT is clinical; that is, severe thrombocytopenia and mucocutaneous hemorrhage in a well-appearing term infant whose mother has a normal platelet count and no history of prior ITP. If maternal platelets are unavailable, administration of IVIG to the neonate usually produces a prompt rise in platelet count. Whichever treatment is used (maternal platelets or IVIG), recurrent thrombocytopenia, albeit with a lesser risk of hemorrhage, may ensue 7 to 10 days later. Therefore, several treatments sometimes are required until the passively acquired antibody disappears by several weeks to months of age. There is no role for corticosteroids in NAIT. Recurrence in subsequent pregnancies is common.

Thrombocytopenia in Older Infants, Children, and Adolescents

Thrombocytopenia is one of the most common hematologic abnormalities encountered in infants, children, and adolescents. The usual mechanisms are decreased platelet production and accelerated destruction (Table 2), either due to antibodies or as a result of nonimmune mechanical factors. Thrombocytopenia due to platelet dilution or loss occurs only in the setting of massive transfusions of packed red blood cells or whole blood (which contains few platelets) after, for example, massive trauma or scoliosis surgery. Thrombocytopenia due to hypersplenism and splenic sequestration virtually always is associated with marked splenomegaly, due most commonly to chronic liver or storage disease. On occasion, splenomegaly and hypersplenism (including thrombocytopenia) oc-

cur due to extrahepatic obstruction, especially portal vein thrombosis.

Thrombocytopenia Due to Decreased Platelet Production

The "well" versus "sick" criteria used in the differential diagnosis of neonatal thrombocytopenia is not as useful in older children. Decreased production of platelets due to diminished megakaryocytes is seen most frequently in acute leukemia or aplastic anemia. Many affected children are not particularly ill on presentation, but physical findings of fever, pallor, lymphadenopathy, or hepatosplenomegaly in addition to the petechiae and ecchymoses should raise suspicion of bone marrow failure rather than ITP. In some children who have marrow injury or replacement, the thrombocytopenia is mild (platelet counts of 50 to 125×10^3/mcL [50 to 125×10^9/L]) and is not associated with bleeding. In this situation, it is particularly important to scrutinize the remainder of the blood count, looking for subtle alterations. Even mild neutropenia or anemia, especially if the red cell mean corpuscular volume (MCV) is elevated, suggests aplastic anemia, myelodysplasia (preleukemia), or frank acute leukemia. In most circumstances in which platelet production is decreased, the platelets are normal in size, as determined by examination of the blood film or electronic measurement of mean platelet volume (MPV) (normal value <10 fL).

If thrombocytopenia due to decreased production is suspected, a bone marrow aspirate and biopsy should be performed. Consultation with a pediatric hematologist is advised. Hemorrhage due to bone marrow failure requires platelet transfusion (approximately 1 U per 5 to 10 kg of body weight) in addition to treatment of the primary disease.

Thrombocytopenia Due to Increased Platelet Destruction

ACUTE ITP. ITP is the most common cause of isolated thrombocytopenia in otherwise well children. This condition occurs at a slightly greater frequency than acute leukemia (approximately 5 in 100,000 children annually) and manifests as a sudden onset of petechiae and bruising (as well as some mucosal hemorrhage in about 30% of patients) in a previously healthy child. ITP is caused by an antiplatelet antibody that binds to the platelet surface and enhances its destruction by Fc receptor-mediated phagocytosis in the spleen and liver. Abnormalities in T cells and inflammatory cytokines also are noted. At least 50% of cases follow a viral infection that is either nonspecific or due, less commonly, to Epstein-Barr, varicella-

zoster, or the human immunodeficiency virus. Some cases occur a few weeks after a live virus vaccination. It has been estimated that 1 in 25,000 children receiving measles-mumps-rubella vaccine develops ITP. The precipitous onset of the bleeding in most children can be very disturbing to the parents. Bleeding manifestations are more subtle and occur insidiously over a period of several weeks to months in approximately 20% of patients.

Physical findings other than the bleeding manifestations are absent. Mild lymphadenopathy or splenomegaly may be due to the viral infection. However, their presence should result in extra attention being devoted to the remainder of the physical examination and the blood count.

The laboratory findings in ITP are those of isolated thrombocytopenia. The platelet count usually is less than 20×10^3/mcL (20×10^9/L) and sometimes is below 5×10^3/mcL (5×10^9/L). The hemoglobin concentration is normal, as is the red cell MCV. The total and differential WBC counts also are normal. Borderline or atypical cases should prompt consideration of marrow failure and referral to a hematologist for performance of a bone marrow aspirate. The peripheral blood smear in children who have ITP is unremarkable except for a paucity of platelets. Platelets that are present are large (MPV of 10 to 15 fL or at least half the diameter of an erythrocyte on the blood film). Children who have substantial epistaxis, menorrhagia, or other mucous membrane hemorrhage (such severe bleeding manifestations are seen in about 3% of patients) also may have anemia due to external blood loss. Intracranial hemorrhage is rare.

Additional laboratory tests usually are not warranted. Results of the PT, PTT, and other blood coagulation tests invariably are normal. A bleeding time test is unnecessary. Antiplatelet antibody testing in the laboratory is unnecessary because the test results lack appropriate diagnostic validity. ITP basically is a diagnosis of exclusion.

Some 75% of children who have ITP have the so-called "acute" form of the disease, which, by definition, resolves spontaneously within 6 months following presentation (and often much sooner). The prominent bleeding tendency apparent at diagnosis usually lessens within 1 to 2 weeks, followed simultaneously or shortly thereafter by a rising platelet count. Bleeding manifestations become less pronounced as the platelet count rises above 20×10^3/mcL (20×10^9/L) and cease with platelet counts higher than 50×10^3/mcL (50×10^9/L) (Table 3).

General management of this self-limited disease in-

cludes avoidance of aspirin and ibuprofen; avoidance of contact sports; limitation of the child's activities (if possible); and most especially, reassurance of the parents regarding the child's recovery and the rarity of serious or life-threatening hemorrhage. The platelets in ITP, having been produced recently in the bone marrow, are large, metabolically active, and "sticky." Therefore, they function well, even when their numbers are markedly reduced. The electronic cell counter often underestimates their actual number because the large platelets sometimes are counted as leukocytes. Unfortunately, most parents and many physicians focus on the platelet count and are extremely alarmed by it and the accompanying manifestations of cutaneous bleeding. This, as well as the desire to "do something," prompts the physician to consider drug treatment aimed at temporarily raising the platelet count.

No treatment alters the natural history of acute ITP, either by preventing its progression to chronicity (ie, lasting >6 mo) or accelerating the disappearance of the offending antiplatelet antibody. However, several drugs are effective in raising the platelet count temporarily by blocking the destruction of antibody-coated platelets by mononuclear phagocytes.

The three treatments employed most commonly are prednisone (or other corticosteroids), IVIG, and anti-D immunoglobulin. The easiest and least expensive of these agents is oral prednisone at a dose of 1 to 2 mg/kg per day (some clinicians use as much as 4 mg/kg per day). Research shows that the platelet count rises more rapidly with steroids than with no drug therapy, although the platelet count declines as the prednisone is tapered (which is necessary within 2 to 3 wk because of toxicity). The adverse effects of prednisone treatment (eg, hyperphagia, irritability, insomnia) often are disconcerting.

IVIG and anti-D immunoglobulin are much more costly and must be administered intravenously. Moreover, both are blood derivatives and, in the past, were associated with the transmission of hepatitis. Most studies show that the platelet count rises more rapidly in children who have ITP following IVIG or anti-D immunoglobulin than with steroids or observation alone. For example, approximately 80% of children receiving IVIG or anti-D immunoglobulin demonstrate a platelet count above 20×10^3/mcL (20×10^9/L) within 3 days and above 50×10^3/mcL (50×10^9/L) within 5 to 7 days. However, no data show that such drug treatment prevents serious bleeding. In addition, their adverse effects are problematic. IVIG often causes headache, nausea, vomiting, and less frequently, aseptic meningitis, allergic reactions, and renal failure. Anti-D immunoglobulin may result in fever and chills and a transient Coombs-positive immune hemolytic anemia.

During the last 3 decades, a raging controversy has evolved among pediatric hematologists regarding whether drug therapy should be administered prophylactically to children who have ITP and exhibit marked thrombocytopenia and cutaneous bleeding alone (or along with minor transient bleeding from the nose or mouth). The "treaters" or "interventionists" focus primarily on the platelet count, aiming to raise it above 20×10^3/mcL (20×10^9/L) as quickly as possible and maintaining it there. The "noninterventionists' or "nontreaters" focus more on bleeding manifestations than on platelet count and believe that the adverse effects, cost, and inconvenience of drug therapy do not warrant its routine use, given the lack of evidence that intracranial or other serious bleeding is prevented. The few controlled trials of therapeutic options in childhood ITP have focused only on platelet count rather than on bleeding severity.

Clearly, the occasional child who has serious hemorrhage should receive either IVIG or anti-D immunoglobulin as well as steroids. Platelet transfusions rarely are indicated in ITP (because they are rapidly destroyed by the circulating antibody) but are warranted in rare instances of life-threatening hemorrhage. Recommended management guidelines from expert panels of American and British pediatric hematologists have been divergent, with the former advocating drug treatment of most children who have newly diagnosed ITP and the latter promulgating observation alone as the best strategy. Additional research is required.

Intracranial hemorrhage (ICH) is the most feared complication of ITP. Its incidence is uncertain, with estimates ranging from 0.5% to 0.1% of cases (1 in 200 to 1 in 1,000). Other than severe thrombocytopenia, risk factors for ICH are poorly defined. ICH may occur either at diagnosis or many months later. There is no evidence that drug therapy prevents ICH. Children who have ITP and headache or other neurologic signs should receive immediate imaging studies and drug therapy. Documented ICH is managed with combined drug treatment, platelet transfusions, neurosurgical intervention, and in some cases, emergency splenectomy. Most children who have ICH survive, although some have persistent neurologic deficits.

CHRONIC ITP. Children whose ITP has lasted longer than 6 months are said to have, by definition, chronic ITP. As with patients who have the acute form of the disease, most otherwise are well and have no underlying

disease. However, some children who have "secondary" chronic ITP have other immunologic disorders such as Evans syndrome (ITP associated with autoimmune hemolytic anemia) or the autoimmune lymphoproliferative syndrome (ALPS) due to impaired B-lymphocyte apoptosis, resulting in unrestrained lymphocyte proliferation. ALPS is familial (autosomal dominant inheritance), often associated with lymphadenopathy and hepatosplenomegaly, and usually results from a mutation in the *fas* gene. In addition, a small percentage of children who apparently have ITP eventually develop systemic lupus erythematosus or another autoimmune condition. Teenagers (especially females) who have apparent chronic ITP should be screened for lupus.

Chronic ITP, like the acute form of the disease, generally is benign and does not require aggressive drug therapy. Most children have platelet counts in the range of 30 to 80×10^3/mcL (30 to 80×10^9/L) and exhibit only bruising and occasional petechiae. The same treatment considerations apply as in acute ITP. Prednisone, IVIG, and anti-D immunoglobulin transiently raise the platelet count but are not curative. However, these agents can be useful at times of elective surgery, following trauma, and for the infrequent child who has severe chronic ITP whose platelet count remains below 20×10^3/mcL (20×10^9/L) associated with prominent cutaneous or mucosal hemorrhage.

Fortunately, most children who have chronic ITP improve over time, with a rising platelet count and cessation of clinically significant hemorrhage. Therefore, chronicity is not synonymous with severe or, necessarily, lifelong disease. Affected children can attend school and participate in virtually all normal childhood activities except for competitive contact sports.

The only proven "curative" treatment for chronic ITP is splenectomy. The spleen is a site of antiplatelet antibody production as well as the major location where antibody-coated platelets are destroyed. Results of splenectomy in children mirror those of adults: 60% to 80% long-term response rate, with normalization of the platelet count. An additional 10% to 15% of patients exhibit at least some improvement, leaving only 5% to 10% of children who exhibit no response. Unfortunately, there are no valid predictors of response to splenectomy in an individual case, although a rise in platelet count following IVIG therapy may have some predictive value.

Splenectomy, usually performed laparoscopically, generally is viewed as a last resort for the child who has ITP, given its invasive and permanent nature. The dreaded complication of splenectomy—overwhelming septicemia due to encapsulated organisms—still repre-

sents a small risk. With prophylactic penicillin (administered for at least 3 y following the procedure) and preoperative immunization against pneumococcus and *Haemophilus influenzae* type b, this complication is extremely rare in current practice. However, life-threatening hemorrhage in chronic ITP also is extremely rare, making it impossible to study the ultimate risks and benefits of splenectomy scientifically. For the rare child who continues to have severe symptomatic ITP following splenectomy (or in situations in which splenectomy is not desired by the treating physician or parents), immunosuppressive agents have been employed. These include cyclophosphamide, azathioprine, cyclosporine, and more recently, rituximab, a chimeric monoclonal antibody against the CD20 antigen present on the surfaces of B cells. Available data do not support the use of these agents outside of a clinical investigative setting.

Other Causes of Acute Thrombocytopenia Due to Increased Destruction

Platelet life span can be shortened by mechanical factors such as damaged vasculature, endotoxin, and consumption along with clotting factors during DIC (Table 2). Children who have most forms of consumptive thrombocytopenia other than ITP are acutely ill with a primary nonhematologic disorder and demonstrate other blood count alterations. This makes the differentiation from ITP usually straightforward. The peripheral blood smear shows large platelets, and response to platelet transfusions is suboptimal. In ill patients of all ages, heparin can cause sudden thrombocytopenia on an immunologic basis. Paradoxically, arterial or venous thrombosis rather than bleeding is a common result. Rarely, consumptive thrombocytopenia can be seen in the Kasabach-Merritt syndrome, in which a giant vascular malformation is present. Such patients may have DIC as well.

Two related conditions–hemolytic-uremic syndrome and thrombotic thrombocytopenic purpura (TTP)–deserve special comment. Both are due to consumption of platelets resulting from endothelial cell injury and vasculitis. In hemolytic-uremic syndrome, which is far more common during childhood, the vascular injury is from toxins derived from certain strains of *Escherichia coli* or other bacteria and involves primarily the kidney and colonic mucosa. The colitis usually causes bloody diarrhea, and the renal failure manifests as oliguria, edema, and hypertension. In addition to laboratory measures of renal impairment and a grossly abnormal urinalysis, microangiopathic hemolytic anemia also is present. Thrombocytopenia at diagnosis often is mild, but platelet counts below 20 to 30×10^3/mcL (20 to 30×10^9/L)

Table 5. Differential Diagnosis of Chronic Thrombocytopenia During Childhood

- Idiopathic thrombocytopenic purpura
- Marrow failure (aplastic anemia, preleukemic states)
- Hypersplenism
- Hereditary thrombocytopenia (dominant and recessive forms, platelet-type and Type 2B von Willebrand disease)
- Drugs (eg, valproic acid)

often are encountered in full-blown disease. Clinical bleeding is uncommon, however, so platelet transfusions usually are unnecessary. Some activation of blood coagulation occurs as well, although DIC is not encountered. TTP is seen primarily in adults. Here, too, the thrombocytopenia is accompanied by microangiopathic hemolytic anemia and some renal impairment. However, central nervous system manifestations (headache, hemiparesis, coma) predominate. This condition results from impaired processing of very high-molecular weight von Willebrand factor multimers released from endothelial cells. Enhanced platelet aggregation and resultant thrombocytopenia ensue. TTP can be chronic or recurrent and usually is due to a mutation in the gene encoding the processing enzyme or an antibody directed against it. Treatment consists of intensive plasmapheresis.

Other Causes of Chronic Thrombocytopenia

As indicated in Table 5, all children who have chronic thrombocytopenia do not have primary or secondary chronic ITP. The differential diagnosis includes bone marrow failure (especially aplastic anemia and myelodysplasia), portal hypertension (suspected when significant splenomegaly is present), and various forms of hereditary thrombocytopenia. Thrombocytopenia may be inherited as a result of a variety of mutations on autosomes or the X chromosome leading to ineffective thrombopoiesis or production of a platelet with an intrinsic defect and a short life span. Many patients have striking abnormalities in platelet size (sometimes they are larger than erythrocytes) or defects affecting other cells or organs. Affected patients may have oculocutaneous albinism, nephritis, hearing defects, or inclusions in their leukocytes. One

form of hereditary thrombocytopenia is Wiskott-Aldrich syndrome, in which eczema and immunodeficiency often accompany X-linked thrombocytopenia. These patients have extremely small platelets (MPV <7 fL).

Thrombocytopenia occasionally is encountered in children receiving various drugs, especially valproic acid and other anticonvulsants. Antineoplastic agents cause thrombocytopenia and suppress other blood elements. Rare inherited metabolic syndromes (eg, isovaleric acidemia) may induce thrombocytopenia by ill-defined mechanisms.

Conclusion

Thrombocytopenia is an important marker of acute or chronic systemic disease as well as a manifestation of certain primary hematologic disorders. Mild thrombocytopenia can be due to serious disease. Hemorrhage does not occur unless the platelet count is less than $50 \times 10^3/$ mcL $(50 \times 10^9/\text{L})$, and serious or life-threatening hemorrhage is infrequent unless the platelet count is less than 10 to $20 \times 10^3/\text{mcL}$ (10 to $20 \times 10^9/\text{L}$). It is important to focus on treating the child rather than on the specific platelet count because rather few platelets are required to protect the child from major hemorrhage.

Suggested Reading

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PIR Quiz
Quiz also available online at www.pedsinreview.org.

5. At times, the pediatrician must discern between the clinical manifestations of bleeding seen in patients who have hemophilia and those seen in a child who has thrombocytopenia. The type of clinical manifestations of bleeding seen in a patient who has classic hemophilia compared with a child who has thrombocytopenia is *most* likely to be:

   A. Central nervous system.
   B. Epistaxis.
   C. Gingival.
   D. Hematuria.
   E. Large joints.

6. A young boy who previously was well has had fever and respiratory symptoms that resolved 10 days ago. His mother has noted that he has had episodes of nosebleeds and bruises on his arms and back over the past 2 days. His pediatrician suspects that this child has a platelet deficiency or platelet function problem. An array of tests can be helpful in assessing this clinical condition. Which one is *most* likely to be no longer helpful in this child's evaluation?

   A. Bleeding time.
   B. Bone marrow examination.
   C. Complete blood count and peripheral smear.
   D. Partial thromboplastin time.
   E. Platelet aggregation.

7. A 32-year-old female who is grava 2 para 1 reports that her first infant had severe bruising and nosebleeds and died of a central nervous system hemorrhage at 5 days of age. You suspect that this first newborn died of neonatal alloimmune thrombocytopenia. Her second infant, for whom you are now caring, has mucous membrane bleeding and petechiae, and a laboratory evaluation demonstrates a platelet count of 5×10^3/mcL (5×10^9/L) at 48 hours of age. The treatment that could help control this infant's bleeding as well as diagnose the cause of the thrombocytopenia is:

   A. Anti-D immunoglobulin.
   B. Corticosteroids.
   C. Exchange transfusion.
   D. Maternal donor platelet transfusion.
   E. Random donor platelet transfusion.

8. A 6-year-old girl who had a previous flulike illness has developed bruising, nose bleeds, and petechial skin lesions over the past 2 days. A detailed physical examination of the child reveals no pallor, lymphadenopathy, or hepatosplenomegaly. A laboratory evaluation at the time of this initial presentation demonstrates a platelet count of 3×10^3/mcL (3×10^9/L). Over the past 6 months, this patient has had several courses of oral steroid therapy and three separate treatments of intravenous gamma globulin with some improvement in her clinical symptoms and platelet count. However, she continues to have low platelet counts (currently at 30×10^3/mcL [30×10^9/L]) along with occasional episodes of epistaxis. Of the following, the *best* approach for this child at this time is:

   A. Cyclophosphamide therapy.
   B. Home schooling.
   C. Low-dose steroid therapy.
   D. No treatment and close follow-up.
   E. Splenectomy.

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