Idiopathic Thrombocytopenic Purpura

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OBJECTIVES

After completing this article, readers should be able to:

1. **Describe the clinical and laboratory features of idiopathic thrombocytopenic purpura (ITP) and explain how they differ in acute and chronic ITP.**
2. **List the features of ITP that distinguish it from other causes of thrombocytopenia.**
3. **Explain the role of bone marrow examination in the diagnosis of ITP.**
4. **Describe the advantages and disadvantages of the primary therapies for ITP.**
5. **Delineate the differences in therapeutic strategies for ITP and neonatal alloimmune thrombocytopenia.**
6. **Describe the role of splenectomy in the treatment of ITP.**

Epidemiology and Pathophysiology

Idiopathic thrombocytopenic purpura (ITP) is an acquired hemorrhagic disorder characterized by: 1) thrombocytopenia that is defined as a platelet count less than 150 x 10^9/L (<150,000/mcL), 2) a purpuric rash, 3) normal bone marrow, and 4) the absence of signs of other identifiable causes of thrombocytopenia. ITP is classified as acute or chronic, with the latter defined as the persistence of thrombocytopenia for more than 6 months from the initial presentation of signs and symptoms.

ITP is estimated to be one of the most common acquired bleeding disorders encountered by pediatricians, with the incidence of symptomatic disease being approximately 3 to 8 per 100,000 children per year. Acute ITP is more prevalent among children younger than 10 years of age, affects males and females equally, and is more prevalent during the late winter and spring. Chronic ITP affects adolescents more often than younger children, with females being affected more frequently than males. Unlike acute ITP, it does not show a seasonal predilection. Patients who have chronic ITP are more likely to exhibit an underlying autoimmune disorder, with up to one third having clinical and laboratory manifestations of collagen-vascular disease.

Although the focus of this article is on the clinical presentation, diagnosis, and management of ITP, the pathophysiology of this condition deserves mention because the mechanisms contributing to thrombocytopenia are more complex than originally thought. It is widely believed that the destruction of platelets in ITP involves autoantibodies to glycoproteins normally expressed on platelet membranes. The spleen and other organs of the reticuloendothelial system subsequently destroy these antibody-coated platelets in a manner analogous to what is observed in autoimmune hemolytic anemia. In addition to increased immune-mediated destruction of platelets, there is evidence that platelet production in ITP is altered, especially in chronic ITP. Although the number of megakaryocytes in the bone marrow are normal or increased in ITP, plasma thrombopoietin levels, which are a measure of proliferation and maturation of megakaryocytic progenitors, are significantly decreased. In chronic ITP, platelet turnover is markedly lower despite decreased platelet survival, and megakaryocytes isolated from affected patients demonstrate suppressed growth in vitro.

The clinical and epidemiological differences between acute and chronic ITP suggest that the resulting thrombocytopenia may have different pathophysiologic mechanisms. In acute ITP, it has been postulated that platelet destruction arises from antibodies generated during the immune response to a viral or bacterial infection that cross-react with platelet antigens. Other mediators of the immune response arising from infection may play an additional role in suppressing platelet production. Chronic ITP, on the other hand, may be a consequence of an inherent defect in immune regulation, as is seen in other autoimmune disorders, resulting in the generation of platelet-specific antibodies. To date, a number of platelet surface glycoproteins (GPs) have been identified as specific targets for autoantibodies in ITP, including GP IIb-IIIa, GP Ib, and GP V. How these antiplatelet antibodies arise in ITP, their significance in distinguishing the pathophysiology of acute versus chronic ITP, and the cellular and biochemical components that are involved in their regulation remain unknown. Current therapeutic regimens used in the management of ITP, therefore, are limited in their efficacy because they fail to target specific immunologic pathways responsible for alteration of platelet production and destruction.

Clinical and Laboratory Features

CLINICAL FINDINGS

ITP is diagnosed largely on clinical findings. Familiarity with the features of acute ITP plays an important role in determining the extent of

ABBREVIATIONS

CBC:	complete blood count
GP:	glycoprotein
ICH:	intracranial hemorrhage
ITP:	idiopathic thrombocytopenic purpura
IVIG:	intravenous immunoglobulins

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the diagnostic evaluation. The typical clinical presentation is that of an otherwise healthy child who develops easy bruising and a purpuric rash. Bleeding from mucous membranes, such as nosebleeds or gingival bleeding, is seen in about one third of cases. Other sites of bleeding include the gastrointestinal tract, vaginal mucosa, the urinary tract, the retina, and conjunctivae. In acute ITP, the onset of signs and symptoms often is preceded by a viral illness. Except for the manifestations of bleeding, findings on the physical examination are otherwise completely normal. Pertinent negatives of the examination include the absence of lymphadenopathy and hepatosplenomegaly. The presence of either should raise the consideration of other diseases, particularly leukemia. Similarly, the presence of pallor, hyperbilirubinemia, and splenomegaly are features of a concomitant hemolytic anemia, which can be seen in conjunction with thrombocytopenia in Evans syndrome and other autoimmune diseases. In chronic ITP, the presentation may be more insidious, and often the patient may be asymptomatic.

The distribution of the patient's bruises and bleeding sites provides additional clues to the etiology. In disorders of primary hemostasis such as ITP and other platelet disorders, bruises are generalized and occur in areas not exposed to trauma. Bruises found in these areas are distinctly abnormal and warrant further investigation. In contrast, bruising in a healthy, active child occurs in exposed areas, especially over hard bony surfaces. Bruising also can be a feature of child abuse, which should be considered in a child who has generalized bruising and a normal platelet count.

LABORATORY FINDINGS

The laboratory features of ITP help to distinguish it from other causes of thrombocytopenia. Key to the laboratory diagnosis of acute ITP is the presence of a low platelet count (usually <20 to 30 x 10^9/L [20,000 to 30,000/mcL]), generally with normal values for age in all other cell lines. In about 15% of patients, mild anemia due to bleeding is present, but red blood cell indices are normal. If results of the complete blood count (CBC) are consistent with ITP, coagulation studies are not warranted. The prothrombin time and partial thromboplastin time are invariably normal, but the bleeding time, which is a direct test of platelet function, almost always is prolonged. Abnormal leukocyte or red blood cell counts should prompt further diagnostic investigation to exclude the possibility of an underlying leukemia or aplastic anemia.

In addition to the CBC, it is essential to examine a peripheral blood smear under light microscopy for several reasons. First, it serves to rule out "pseudothrombocytopenia," an in vitro artifact caused by the clumping of platelets in tubes containing the anticoagulant ethylenediamine-tetraacetic acid, which results in low platelet counts when measured on an automated cell counter. Second, characterization of red blood cell morphology enables the examiner to detect the presence of a concomitant hemolytic process (eg, hemolytic-uremic syndrome, disseminated intravascular coagulation, or Evans syndrome) or hypoproliferative anemia (eg, anemia due to nutritional deficiencies). Third, abnormal white blood cell counts or the presence of immature nucleated forms may indicate an underlying primary or secondary bone marrow neoplasm. Fourth, examination of individual platelets aids in the diagnosis of ITP. Platelet size is increased noticeably in acute ITP, reflecting increased platelet turnover and the release of younger, larger platelets from the bone marrow, while it may be reduced in other thromboctyopenic entities (see Differential Diagnosis).

An examination of the bone marrow is indicated in certain situations (see following section). Megakaryocytes usually are present in normal or increased numbers in acute ITP. Bone marrow examination also is useful in confirming normal morphologies in other cell types and in ascertaining the presence of blast cells suggestive of leukemia or other lymphoproliferative disorders. Finally, it can help to determine the presence of metastatic disease, such as neuroblastoma.

In chronic ITP, the platelet count at presentation is generally between 20 and 70 x 10^9/L (20,000 and 70,000/mcL). Additional tests should be performed before making the diagnosis of chronic ITP, including a evaluation for autoimmune disease, infection, and immunodeficiency (Table 1). Thyroid studies are obtained to rule out autoimmune thyroid disease, which has been associated with chronic ITP.
A Coombs test and measurement of the reticulocyte count are employed to exclude Evans syndrome (immune thrombocytopenia with autoimmune hemolytic anemia). Numerous viral infections have been implicated in causing thrombocytopenia. Isolated thrombocytopenia can be the presenting symptom of human immunodeficiency virus infection and may be seen after immunization with measle-mumps-rubella vaccine.

TABLE 1. Laboratory Tests in the Evaluation of Chronic Immune Thrombocytopenic Purpura

Autoimmune Disease
• Antinuclear antibody
• Anti-DNA antibody
• Antiphospholipid antibody
• Sedimentation rate
• Coombs test/reticulocyte count
• Thyroid studies (if thyroid disease is suspected)
Infection
• Human immunodeficiency virus (HIV)
• Cytomegalovirus titers
• Epstein-Barr virus titers
• Consider other viral etiologies (less common):
—Rubella
—Measles
—Varicella
—Mumps
—Hepatitis
Immunodeficiency
• HIV titer
• Quantitative immunoglobulins
• Quantitation of T and B cell subsets

The Role of Bone Marrow Aspirations in Diagnosis

Whether bone marrow should be examined routinely in patients who have suspected ITP is controversial. Historically, such examinations were common to rule out diseases such as leukemia and aplastic anemia as causes of the thrombocytopenia. However, there is increasing argument against performing bone marrow aspirations to diagnose acute ITP. As stated previously, acute ITP is largely a clinical diagnosis that is confirmed relatively easily by routine blood tests. A growing number of studies have demonstrated that the likelihood of a newly diagnosed leukemia presenting as an isolated thrombocytopenia is extremely low. Among 2,239 patients newly diagnosed with acute lymphoblastic leukemia in a recent Pediatric Oncology Group study population, for example, none exhibited isolated thrombocytopenia in the presence of an otherwise normal CBC and cell morphologies on peripheral smear. In a retrospective review of 127 cases of children who had an initial diagnosis of acute ITP and in whom confirmatory bone marrow aspirations were performed, only five cases were identified where examination of the bone marrow led to a different diagnosis from ITP. In each of these five cases, features on initial clinical presentation were atypical for acute ITP. A more recent review of 322 cases of children who had provisional diagnoses of acute ITP confirmed by bone marrow aspiration also failed to reveal a single case of leukemia.

Furthermore, the decision to perform a bone marrow aspiration can be deferred if a patient is to be treated initially with intravenous immunoglobulins (IVIG) pending the response to treatment. This approach avoids the concern of interfering with the diagnosis of leukemia by partially treating a patient who presumably has ITP with steroids.

Even though bone marrow examinations have apparent limited value in the diagnosis of acute ITP, they must be performed in situations where the diagnosis does not absolutely correlate with the expected clinical and laboratory findings (see Differential Diagnosis). These include: 1) unusual findings on history and physical examination (eg, history of fevers, weight loss, fatigue, bone pain, and presence of lymphadenopathy or splenomegaly on physical examination); 2) the presence of abnormal white or red blood cell counts and indices on the CBC; and 3) cases in which steroids are to be used for treatment, either as a first-line drug or as a second option when IVIG fails to resolve the thrombocytopenia. Bone marrow examination is also important in evaluating chronic ITP and in cases of thrombocytopenia that are refractory to multiple treatment modalities. The importance of performing bone marrow aspirations in these circumstances is highlighted by case reports in which the diagnosis of leukemia or aplastic anemia not only was delayed, but it was masked by the partial treatment with steroids of patients initially diagnosed as having ITP.

Although examination of the bone marrow is the "gold standard" in diagnosing acute ITP, noninvasive tests to distinguish acute ITP from other thrombocytopenic disorders continue to be developed and may decrease further the need to perform bone marrow aspirations. None is in general clinical use to date, but they show promise as useful adjuncts to other laboratory tests for diagnosing ITP. One such method involves measurement of the reticulated platelet count. As mentioned previously, platelets on the peripheral blood smear from patients who have acute ITP are larger, indicating increased platelet turnover and a higher percentage of young platelets in the circulation. These platelets contain a higher RNA content than do more mature platelets, as do immature red blood cells (ie, reticulocytes). These platelets have been termed "reticulated platelets." By employing fluorescent dyes that bind nucleic acid and measuring dye fluorescence by flow cytometry, it is possible to quantitate reticulated platelets and distinguish between a hyperproliferative (eg, acute ITP) and a hypoproliferative (eg, leukemia, aplastic anemia) process. Comparison of the reticulated platelet count in 15 patients who had acute ITP, 20 patients who had acute lymphoblastic leukemia, 10 patients who had aplastic anemia, and 27 healthy children revealed a significantly higher count among those who had acute ITP compared with the other groups. Importantly, the degree of elevation in the reticulated platelet count in acute ITP is such that there was no overlap with the hypoproliferative groups, providing a positive predictive value, sensitivity, and specificity approaching 100% when the reticulated platelet count exceeded 13.7% and the total platelet count was less than 50 x 10^9/L (50,000/mcL). Tests such as this potentially can assist in the diagnosis of ITP without the need to perform more invasive procedures. Its utility in distinguishing acute ITP from other non-neoplastic causes of thrombocytopenia and its role in the diagnosis of chronic ITP, however, warrant further investigation.

Differential Diagnosis

The differential diagnosis for thrombocytopenia is very broad. A low platelet count can result from immunologic and nonimmunologic entities. Table 2 lists selected causes of thrombocytopenia and the clinical and laboratory associations that distinguish them from ITP. It is worth stressing again that the diagnosis of ITP is based on the presence of an isolated thrombocytopenia in the absence of clinical and laboratory features suggestive of other disorders. The distinction of these diseases from ITP is based almost entirely on findings from the history and physical examination and interpretation of the CBC. As stated previously, ordering additional tests or examining the bone marrow usually is not necessary to establish the diagnosis of ITP.

Management of Acute ITP

Acute ITP generally can be diagnosed and managed in an outpatient setting by the primary care pediatrician. Referral to a hematologist-oncologist is warranted if there is evidence of concurrent disease, such as malignancy, bone marrow failure, autoimmune disease, or immunodeficiency.

TABLE 2. Differential Diagnosis of Thrombocytopenia

DISORDER	ASSOCIATED CLINICAL FEATURES	LABORATORY FEATURES
Decreased Platelet Production		
Congenital		
• Thrombocytopenia-Absent Radius (TAR) syndrome	• Absence of radii at birth • Other skeletal anomalies may be present • Congenital heart disease associated in one third of cases	• Platelet count usually 15 to 30 × 10^9/L (15,000 to 30,000/mcL)
• Fanconi anemia	• Short stature • Skin hyperpigmentation • Hypoplasia of thumb and radii • Renal abnormalities may be present • Microcephaly • Microphthalmia	• Pancytopenia due to aplastic anemia
• Amegakaryocytic thrombocytopenia	• Absence of skeletal abnormalities seen in TAR syndrome	• Thrombocytopenia present in the neonatal period
Acquired		
• Leukemia	• History of chronic fatigue, fevers, weight loss, pallor, bone pain • Lymphadenopathy • Splenomegaly • Hepatomegaly may be present	• Elevated white blood cell count • Anemia • Blast cells on peripheral smear (ie, leukoerythroblastosis)
• Aplastic anemia	• History of fatigue, bleeding, or recurrent infection • Physical examination findings nonspecific • Absence of splenomegaly	• Pancytopenia • Severe neutropenia • Low reticulocyte count
• Neuroblastoma	• Abdominal mass in majority of cases • Presence of paraneoplastic syndromes • Neurologic manifestations from spinal cord involvement	• Thrombocytopenia due to bone marrow metastasis
• Nutritional deficiency	• History of poor nutrition or specialized diets • Pallor, weakness, and fatigue due to anemia • Neurologic deficits in vitamin B_{12} deficiency	• Megaloblastic anemia present • Hypersegmented neutrophils on peripheral smear • Low reticulocyte count • Low vitamin B_{12} or folate levels
• Drugs (see Table 3)	• History of drug use or recent change in dose	
Increased Platelet Destruction		
Immune		
• Neonatal allommune thrombocytopenia	• Generalized petechiae within first several hours of birth	• Platelet count in mother is normal
• Drugs (see Table 3)	• History of drug use or recent change in dose	
• Human immunodeficiency virus (HIV) infection	• Systemic signs and symptoms of HIV infection	• Abnormalities in any or all cell lineages • HIV serologies confirm the diagnosis

TABLE 2. Continued

DISORDER	ASSOCIATED CLINICAL FEATURES	LABORATORY FEATURES
• Posttransfusion purpura	• History of platelet transfusion a few hours prior to thrombocytopenia	• Acute marked thrombocytopenia
• Collagen-vascular disease/ autoimmune disease	• Systemic manifestations, including joint pain/swelling, dermatologic findings	• Anemia of chronic disease usually present • White blood cell counts occasionally abnormal
Nonimmune • Hemolytic-uremic syndrome	• History of bloody diarrhea (from *Escherichia coli* O157:H7, *Shigella* sp) • Renal failure	• Microangiopathic microcytic anemia on peripheral smear
• Disseminated intravascular coagulation	• Signs and symptoms of sepsis (eg, fever, tachycardia, hypotension)	• Prothrombin time and partial thromboplastin time are elevated • Microangiopathic microcytic anemia on peripheral smear • Fibrinogen level decreased • D-dimers present
• Cyanotic heart disease	• Cyanosis • Congestive heart failure	• Compensatory polycythemia
Qualitative Platelet Disorders • Wiskott-Aldrich syndrome	• X-linked inheritency pattern • Eczema • Recurrent infections due to immunodeficiency	• Platelet count 20 to 100 $\times$ 10^9/L (20,000 to 100,000/mcL) • Platelets very small on peripheral smear
• Bernard-Soulier syndrome	• Autosomal dominant inheritance pattern • Ecchymoses and gingival and gastrointestinal bleeding common	• Large platelets on peripheral smear, occasionally larger than lymphocytes
• May-Hegglin anomaly	• Autosomal dominant inheritance pattern • Most patients asymptomatic	• Giant platelets on peripheral smear • Inclusion bodies present in leukocytes (Döhle bodies)
• Gray platelet syndrome	• Bleeding, usually mild	• Platelets on peripheral smear appear pale and oval
Sequestration • Kasabach-Merritt syndrome	• Rapid increase in size of a hemangioendothelioma occurring in the neonatal period	
• Hypersplenism	• History of liver disease/portal hypertension • Splenomegaly on physical examination	• Concomitant anemia and abnormal leukocyte count, depending on the disease • Associated with leukemia and other infiltrative disease

SUPPORTIVE MEASURES

Supportive measures are important in the management of acute ITP. These include restricting physical activity, wearing protective headgear, lining the crib with protective padding, avoiding medications that suppress platelet production or alter their function (Table 3), and maintaining a low threshold for prompt evaluation of the child who has thrombocytopenia and sustains blunt head or abdominal trauma.

PHARMACOLOGIC MANAGEMENT

The pharmacologic management of acute ITP continues to be the subject of much controversy because most cases of ITP are self-limited; 80% to 90% of patients will make a

TABLE 3. Common Drugs and Thrombocytopenia

Drugs Associated With Decreased Platelet Production
• Chemotherapeutic agents
• Thiazide diuretics
• Alcohol
• Estrogen
• Chloramphenicol
• Ionizing radiation
Drugs Associated With Increased Platelet Destruction
• Sulfonamides
• Quinidine
• Quinine
• Carbamazepine
• Valproic acid
• Heparin
• Digoxin
Drugs Associated With Altered Platelet Function
• Aspirin
• Dipyridamole

full and sustained recovery within 6 months without any treatment. However, at present there are no definitive diagnostic predictors to enable the physician to identify the 10% to 20% of patients who will progress to chronic ITP. Moreover, patients who have extremely low platelet counts (ie, $<$10 to 20 x 10^9/L [10,000 to 20,000/mcL]) are at increased risk for significant bleeding, the most devastating of which is intracranial hemorrhage (ICH). ICH always should be considered in the patient who has thrombocytopenia and presents with a persistent headache. Although the incidence of ICH is extremely low (only 56 documented cases identified from 1975 to 1996), the mortality rate is significant (46%), and virtually all episodes have been associated with platelet counts of less than 2 x 10^9/L (20,000/mcL). Thus, the rationale for aggressive treatment of severe ITP at the time of diagnosis is to raise the platelet count to a level that decreases the risk of significant bleeding events.

IVIG and Steroids

Currently, the mainstays of pharmacologic management for acute ITP are IVIG and corticosteroids. The ability of both of these agents to raise platelet counts has been documented in multiple studies, with mean time to raise platelet counts 20 x 10^9/L (20,000/mcL) ranging from 24 to 72 hours after initiation of therapy. There currently are no clear criteria for selecting IVIG or steroids as a first-line agent. IVIG has several advantages over steroids. First, it appears to induce a more rapid increase in platelet count. Second, the adverse effects of steroid use, including weight gain, hypertension, hyperglycemia, Cushing syndrome, osteoporosis, and psychological disorders, are avoided with IVIG. Third, the physician can begin a therapeutic trial with IVIG without bone marrow aspiration to rule out leukemia.

The disadvantages of IVIG as a first-line agent include its higher cost and difficulty with administration. It requires intravenous access, and the infusion requires several hours of observation. Moreover, IVIG is associated with a number of adverse effects. An aseptic meningitis effect will produce symptoms similar to that of an acute ICH, leading to additional costly tests to differentiate these two diagnoses. In a recent study examining 38 children who had acute ITP treated with IVIG, 34% had neurologic complications, and virtually all of those affected required hospitalizations for a period longer than what was required for the ITP alone. Twenty-four percent of these patients required emergent computed tomography to rule out ICH. The combination of prolonged hospitalization and additional diagnostic studies resulted in an increased cost of approximately $1,700 for each patient who experienced neurologic side effects from IVIG.

ANTI-Rh(D)

Another agent under investigation in the treatment of acute ITP is anti-Rh(D). It is less expensive than IVIG and has been shown to raise platelet counts effectively. However, it is useful only in patients who are Rh-positive, and hemolytic anemia can occur as a side effect. In some published reports, treatment with anti-Rh(D) resulted in a slower rise in platelet count than with steroids or IVIG, which theoretically could prolong the interval in which a patient is at risk for ICH. However, other studies have shown that an increased dose of anti-Rh(D) raised platelet counts as quickly as did IVIG; the length of hospital stay was identical for patients receiving anti-Rh(D) and IVIG.

DOSING

Dosing schedules for IVIG and steroids are highly variable (Table 4). IVIG in a dose of 0.25 to 1 g/kg per day for two consecutive days or as a single dose of 0.8 g/kg has been shown to increase platelet counts. Dosage recommendations for oral prednisone vary even more, ranging from 4 mg/kg per day for 4 days with or without a subsequent taper to 2 mg/kg per day for 2 to 3 weeks. Some investigators also have demonstrated a role for high-dose intravenous methylprednisone (30 mg/kg per day for 2 to 3 days) in raising platelet counts. Anti-Rh(D), in the comparison trials with IVIG and prednisone, was administered intramuscularly in doses of 25 to 50 mcg/kg per day for two consecutive days. It is important to note that the schedules listed in Table 4 are based on studies involving relatively few patients. The results of large, randomized, and controlled studies to establish the optimal doses of IVIG, steroids, and anti-Rh(D) have yet to be published.

Although IVIG, steroids, and

TABLE 4. Selected Dosing Schedules for Therapy of Acute ITP

DRUG	DOSE SCHEDULES
Oral prednisone	2 mg/kg per day for 14 to 21 days 60 mg/m^2 per day for 21 days 4 mg/kg per day for 7 days, followed by 14-day taper
Intravenous methylprednisolone	10 to 30 mg/kg per day for 3 to 5 days
IVIG	0.8 g/kg per dose for 1 dose 1 g/kg per day for 2 days 250 mg/kg per day for 2 days 400 mg/kg per day for 2 days 500 mg/kg per day for 2 days 0.4 g/kg per day for 5 days
Anti-Rh(D)	25 mcg/kg per day for 2 days 45 to 50 mcg/kg per day for 2 days

anti-Rh(D) have been shown to shorten the duration of thrombocytopenia, it is essential to realize that *they are not cures for ITP*. They only have the potential to shorten the period of thrombocytopenia and minimize the risk of life-threatening bleeding events. As stated previously, ITP is a self-limited disease in most pediatric patients. All of the studies performed to date on the treatment of acute ITP have focused on a rise in platelet counts as the endpoint; no studies have documented decreases in morbidity or mortality. Accordingly, despite the existence of agents that can raise the platelet count, a number of important questions remain: 1) Are there factors other than platelet counts less than 20 x 10^9/L (20,000/mcL) that contribute to an increased risk of intracranial hemorrhage? 2) What is the cost-effectiveness of treating patients who have acute ITP with IVIG versus steroids versus anti-Rh(D), given each agent's advantages and disadvantages? 3) How effective are these agents in the prevention of chronic ITP?

Neonatal Thrombocytopenia

Immune thrombocytopenia can be manifested during the neonatal period in infants born to mothers who have ITP and, much more rarely, in neonatal alloimmune thrombocytopenia. In the latter, which occurs in approximately 1 in 5,000 newborns, the platelets of the affected infant contain different antigens from those of the mother, and the subsequent formation of maternal alloantibodies that cross the placenta result in platelet destruction. Both diseases are self-limiting; in most cases, the thrombocytopenia resolves within 6 weeks of birth. However, there are significant differences between the two diseases that deserve mentioning. First, determining the maternal history is essential in distinguishing between the two diagnoses. In maternal ITP, the mother's platelet count is generally below normal, and in most cases there is a well-documented history of chronic ITP. In neonatal alloimmune thrombocytopenia, the mother has a normal platelet count and has no history of immune thrombocytopenia. However, a history of a sibling who has neonatal thrombocytopenia is strongly suggestive of neonatal alloimmune thrombocytopenia because subsequent affected siblings are affected more severely than the first. Second, neonatal alloimmune thrombocytopenia is a far more serious disorder. Not only is the platelet count lower compared with that of the infant born to a mother who has ITP, but the incidence of ICH is significantly higher (10% to 30% versus 1% in infants born to mothers who have ITP).

The management of the infant who has autoimmune or alloimmune thrombocytopenia is similar. IVIG, steroids, platelet transfusions, and exchange transfusions all have been investigated. The important distinction in treatment is that in neonatal alloimmune thrombocytopenia, plasmapheresed or washed platelets from the mother should be used for transfusion because they lack the alloantigen responsible for the formation of antiplatelet antibodies. In infants born to mothers who have ITP, transfusion with maternal platelets is avoided because they contain the antigens responsible for the formation of platelet autoantibodies. Furthermore, because most cases of neonatal thrombocytopenia due to maternal ITP are mild and self-limiting, aggressive therapy usually is not required.

Management of Chronic ITP

In the minority of cases in which thrombocytopenia persists for more than 6 months (ie, chronic ITP), management is highly individualized and depends primarily on the degree of thrombocytopenia and the need to preserve the patient's quality of life. Studies examining the natural course of chronic ITP suggest that most patients maintain platelet counts above 30 x 10^9/L (30,000/mcL). In a significant percentage of patients (40% to 79%), complete remission (defined as a platelet count $>$100 x 10^9/L [100,000/mcL]) is achieved over the course of 3 months to 15 years. As in acute ITP, the goal of management is to minimize the risk of significant bleeding. Patients should be directed to avoid activities that increase the risk of trauma and to avoid all medications that suppress platelet production and function (Table 3). Platelet counts must be monitored regularly because this may determine the aggressiveness of further treatment. Finally, patients should be evaluated for autoimmune disease as previously described because a greater percentage of patients who have features of chronic ITP have an underlying autoimmune disorder. It is important to re-evaluate these patients over time if the initial evaluation fails to establish a diagnosis. In some cases, the diagnosis may not be apparent for years.

PHARMACOLOGIC OPTIONS

Pharmacologic approaches to the management of chronic ITP that have been studied to date include steroids, IVIG, androgens, anti-Rh(D), recombinant human interferon-alpha-2b, and immunosuppressive agents used alone or in combination. Although all of these have been shown to induce a transient rise in platelet counts, none has demonstrated an ability to sustain a desirable platelet count; therefore, repeated treatments may be required. This not only potentiates chronic drug toxicity, but it greatly increases the cost of therapy. Whether any of these agents alters the natural course of chronic ITP, affects long-term morbidity or mortality, or increases the rate of long-term remission remains unclear. Because the majority of cases of chronic ITP remit either spontaneously or with treatment and because the associated mortality and morbidity are low, a number of authors advocate interventions only when the platelet count is dangerously low or if the patient is symptomatic.

SPLENECTOMY

Splenectomy has been shown to induce long-term remission in chronic steroid/IVIG-resistant ITP. The benefits of splenectomy over long-term drug therapy include the avoidance of chronic drug toxicity and potentially greater cost-effectiveness. However, splenectomy entails inherent risks of morbidity and mortality. Postsurgical hemorrhage and postsplenectomy sepsis are two of the life-threatening complications. Although the risk of postoperative bleeding is surprisingly low, the risk of postsplenectomy sepsis is significant, with the incidence of septic mortality ranging from 3% to 11%. Furthermore, the incidence of postsplenectomy sepsis is highest among patients younger than 5 years of age. Causative organisms include pneumococcus, *Haemophilus influenzae*, and meningococcus. Immunization with pneumococcal, *Haemophilus*, and meningococcal vaccines before splenectomy, administration of prophylactic antibiotic therapy, and delay of splenectomy for as long as possible for patients in the high-risk age group are recommended to minimize the risk of postsplenectomy sepsis.

Splenectomy does not ensure long-term remission in all patients; only 60% to 90% of those who have chronic ITP respond to splenectomy. The need to identify patients who are likely to respond to splenectomy is abundantly clear. Results of several retrospective studies have shown that those who demonstrated a significant, although transient, rise in platelet count after treatment with either steroids or IVIG had a good response to splenectomy (ie, they did not require any subsequent medical therapy for their thrombocytopenia). In contrast, those who did not respond well initially to medical therapy had relatively poor responses to splenectomy and required continuing medical management.

Splenectomy is reserved for those patients who have extremely low platelet counts (and, therefore, are at increased risk of bleeding) and who are refractory to pharmacologic management. In cases of life-threatening hemorrhage due to ITP, emergent splenectomy may be required to increase the platelet count rapidly. It is important to remember that platelet transfusions alone prior to splenectomy, although helpful, will not raise the platelet count. IVIG and steroids also are required to disrupt the autoimmune destruction of platelets and maintain the platelet count at a level desirable for surgery. A noninvasive alternative to splenectomy in the treatment of chronic ITP is the use of a short course of radiation therapy, which resulted in a sustained increase in platelet counts in a small group of older adult patients who were considered too unstable for surgery. Use of this therapeutic approach in the pediatric population remains to be evaluated.

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SUGGESTED READING

Aronis S, Platolouki H, Mitsika A, Haidas S, Constantopoulos A. Seventeen years of experience with chronic idiopathic thrombocytopenic purpura in childhood. Is therapy always better? *Pediatr Hematol Oncol.* 1994;11:487–498

Beardsley DS, Nathan DG. Platelet abnormalities in infancy and childhood. In: Nathan DG, Oski FA, eds. *Hematology of Infancy and Childhood*. Philadelphia, Penn: WB Saunders; 1998:1585–1630

Blanchette V, Imbach P, Andrew M, et al. Randomised trial of intravenous immunoglobulin G, intravenous anti-D, and oral prednisone in childhood acute immune thrombocytopenic purpura. *Lancet.* 1994; 344:703–707

Blanchette VS, Luke B, Andrew M, et al. A prospective, randomized trial of high-dose intravenous immune globulin G therapy, oral prednisone therapy, and no therapy in childhood acute immune thrombocytopenic purpura. *J Pediatr.* 1993;123: 990–995

Bolton-Maggs PH, Moon I. Assessment of UK practice for management of acute childhood immune thrombocytopenic purpura against published guidelines. *Lancet.* 1997;350:620–623

Borgna-Pignatti C, Battisti L, Zecca M, Locatelli F. Treatment of chronic childhood immune thrombocytopenic purpura with intramuscular anti-D immunoglobulins. *Br J Haematol.* 1994; 88:618–620

Buchanan GR. ITP. How much treatment is enough? *Contemporary Pediatrics* 1995; 12:23–48

Buchanan GR, Holtkamp CA. Prenisone therapy for children with newly diagnosed idiopathic thrombocytopenic purpura. *Am J Pediatr Hematol Oncol.* 1984;6:355–361

Bussel JB. Immune thrombocytopenia in pregnancy: autoimmune and alloimmune. *J Repro Immunol.* 1997;37:35–61

Bussel JB, Corrigan JJ. Platelet and vascular disorders. In: Miller DR, Baehener RL, eds. *Blood Disease of Infancy and Childhood*. 7th ed. St. Louis, Mo: Mosby; 1995: 878–886

Calpin C, Dick P, Poon A, Feldman W. Is bone marrow aspiration needed in acute childhood idiopathic thrombocytopenic purpura to rule out leukemia? *Arch Pediatr Adolesc Med.* 1998;152:345–347

Calverley DC, Jones GW, Kelton JG. Splenic radiation for corticosteroid-resistant immune thrombocytopenia. *Ann Intern Med.* 1992;116(12 pt1):977–981

Carcao MD, Zipursky A, Butchart S, Leaker M, Blanchette VS. Short-course oral prednisone therapy in children presenting with acute immune thrombocytopenic purpura (ITP). *Acta Paediatr.* 1998;424(suppl): 71–74

Davis PW, Williams DA, Shamberger RC. Immune thrombocytopenia: surgical therapy and predictors of response. *J Pediatr Surg.* 1991;26:407–413

Dubansky SA, Boyett JM, Falletta J, et al. Isolated thrombocytopenia in children with acute lymphoblastic leukemia: a rare event in a pediatric oncology group study. *Pediatrics.* 1989;84:1068–1071

Ein SH. Splenic lesions. In: Ashcraft KW, Holder TM, eds. *Pediatric Surgery*. Philadelphia, Penn: WB Saunders; 1993: 535–545

Emmons RV, Reid DM, Cohen RL, et al. Human thrombopoietin levels are high when thrombocytopenia is due to megakaryocyte deficiency and low when due to increased platelet destruction. *Blood.* 1996;87:4068–4071

Fujimura K, Takafuta T, Kuriya S, et al. Recombinant human interferon alpha-2b (rh IFN alpha-2b) therapy for steroid resistant idiopathic thrombocytopenic purpura. *Am J Hematol.* 1996;51:37–44

Graziano SL. Thrombocytopenia due to enhanced platelet destruction by immunologic mechanisms. In: Williams WJ, ed. *Hematology*. New York, NY: McGraw Hill; 1996

Halperin DS, Doyle JJ. Is bone marrow examination justified in idiopathic thrombocytopenic purpura? *Am J Dis Child.* 1988;142:508–511

Kattamis AC, Shankar S, Cohen AR. Neurologic complications of treatment of childhood acute immune thrombocytopenic purpura with intravenously administered immunoglobulin G. *J Pediatr.* 1997;130: 281–283

Kuhne T, Elinder G, Blanchette VS, Garvey B. Current management issues of childhood and adult immune thrombocytopenic purpura (ITP). *Acta Paediatr.* 1998; 424(suppl):75–81

Kuhne T, Freedman J, Semple JW, Doyle J, Butchart S, Blanchette VS. Platelet and immune responses to oral cyclic dexamethasone therapy in childhood chronic immune thrombocytopenic purpura. *J Pediatr.* 1997;130:17–24

Kurtzberg J, Stockman JA. Idiopathic autoimmune thrombocytopenic purpura. *Adv Pediat.* 1994;41:111–134

Law C, Maraccio M, Tam P, Heddle N, Kelton JG. High-dose intravenous immune globulin and the response to splenectomy in patients with idiopathic thrombocytopenic purpura. *N Engl J Med.* 1997;336: 1494–1498

Lilleyman JS. Intracranial haemorrhage in idiopathic thrombocytopenic purpura. Paediatric Haematology Forum of the British Society for Haematology. *Arch Dis Child.* 1994;71:251–253

Medeiros D, Buchanan GR. Current controversies in the management of idiopathic thrombocytopenic purpura during childhood. *Pediat Clin North Am.* 1996;43: 757–171

Parker RI, Siegel RS, Ratajczak MZ, Gewirtz AM. Deficient in vitro megakaryocytopoiesis and decreased in vivo platelet turnover in children and young adults with chronic thrombocytopenia. *J Pediatr Hematol Oncol.* 1998;20:196–201

Reid MM. Bone marrow examination before steroids in thrombocytopenic purpura or arthritis. *Acta Paediat.* 1992;81:1052–1053

Reid MM. Chronic idiopathic thrombocytopenic purpura: incidence, treatment, and outcome. *Arch Dis Child.* 1995;72:125–128

Rosthøj S, Nielsen S, Pedersen FK. Randomized trial comparing intravenous immunoglobulin with methylprednisolone pulse therapy in acute idiopathic thrombocytopenic purpura. Danish ITP Study Group. *Acta Paediatr.* 1996;85:910–915

Saxon BR, Blanchette VS, Butchart S, Lim-Yin J, Poon AO. Reticulated platelet counts in the diagnosis of acute immune thrombocytopenic purpura. *J Pediatr Hematol Oncol.* 1998;20:44–48

Schultz KR, Strahlendorf C, Warrier I, Ravindranath Y. Cyclosporin A therapy of immune-mediated thrombocytopenia in children. *Blood.* 1995;85:1406–1408

Tamary H, Kaplinsky C, Levy I, et al. Chronic childhood idiopathic thrombocytopenia purpura: long-term follow-up. *Acta Paediatr.* 1994;83:931–934

Tarantino MD, Madden RM, Fennewald DL, Patel CC, Bertolone SJ. Treatment of childhood acute immune thrombocytopenic purpura with anti-D immune globulin or pooled immune globulin. *J Pediatr.* 1999; 134:21–26

Van Hoff J, Ritchey AK. Pulse methylprednisolone therapy for acute childhood idiopathic thrombocytopenic purpura. *J Pediatr.* 1988;113:563–566

Walker RW, Walker W. Idiopathic thrombocytopenia, initial illness and long term follow up. *Arch Dis Child.* 1994;59:316–322

Warrier I, Bussel JB, Valdez L, Barbosa J, Beardsley DS. Safety and efficacy of low-dose intravenous immune globulin (IVIG) treatment for infants and children with immune thrombocytopenic purpura. Low-Dose IVIG Study Group. *J Pediatr Hematol Oncol.* 1997;19:197–201

Winiarski J. Mechanisms in childhood idiopathic thrombocytopenic purpura (ITP). *Acta Paediatr.* 1998; 424(suppl):54–56

PIR QUIZ

Quiz also available online at www.pedsinreview.org.

14. Neonatal alloimmune thrombocytopenia and neonatal autoimmune thrombocytopenia are similar in that both:
    A. Are associated with previous siblings being affected by the disease.
    B. Are self-limiting.
    C. Have maternal platelet counts in the same range.
    D. Occur primarily in infants born to mothers who have immune thrombocytopenia purpura.
    E. Resolve within 7 to 10 days after birth.

15. Which endocrine disorder has been associated with chronic immune thrombocytopenia purpura (ITP)?
    A. Addison disease.
    B. Autoimmune thyroid disease.
    C. Congenital adrenal hyperplasia.
    D. Hyperparathyroidism.
    E. Hypopituitarism.

16. A 32-year-old woman has just delivered her third child. Both of her previous children were diagnosed as having neonatal alloimmune thrombocytopenia that required treatment. Findings on the physical examination of the newborn are unremarkable except for a few petechiae on his arms and legs. A complete blood count is unremarkable except for a platelet count of 30 x 10^9/L (30,000/mcL). The *best* treatment for this child's ITP is:
    A. Anti-Rh(D).
    B. Corticosteroids.
    C. Intravenous immunoglobulin.
    D. None.
    E. Plasmapheresed maternal platelets.

17. A 4-year-old girl presents with a 1-week history of extensive bruising of the arms and legs and intermittent episodes of epistaxis. Physical examination reveals large palpable bruises on both arms and legs and crusted blood in the nares. A complete blood count reveals a white blood cell count of 10.5 x 10^9/L (10.5 x 10^3/mcL), hemoglobin of 6.51 mmol/L (10.5 g/dL), hematocrit of 0.32 (32%), and platelet count of 20 x 10^9/L (20,000/mcL). The differential count includes 80% segmented forms, 8% bands, 12% lymphs, and a blood smear with normal red blood cell morphology and decreased platelets. The platelets that are visualized are large. You decide to initiate treatment for suspected acute ITP with intravenous immunoglobulin (IVIG). The *primary* advantage of using IVIG over corticosteroids to treat this child's acute ITP is:
    A. Cost of administration.
    B. Ease of administration.
    C. Lack of complications.
    D. More rapid increase in the platelet count.
    E. Ready availability for administration.

18. You hospitalized a 4-year-old child with a diagnosis of acute ITP. On admission, the child had a platelet count of 20 x 10^9/L (20,000/mcL). Initial treatment is an infusion of IVIG. A repeat platelet count 4 days later shows a platelet count of 22 x 10^9/L (22,000/mcL). However, the following day the patient suddenly develops confusion and somnolence. Physical examination reveals increased numbers of petechiae on the trunk and ecchymoses at the venipuncture sites. Your next step should include all of the following *except*:
    A. Consulting neurology for further evaluation.
    B. Initiating a transfusion of platelets.
    C. Obtaining a STAT complete blood count with platelets.
    D. Obtaining immediate computed tomography of the head.
    E. Starting antibiotics at the appropriate doses to treat possible meningococcemia.

Idiopathic Thrombocytopenic Purpura

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