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Idiopathic thrombocytopenic purpura (ITP) is the most common acquired bleeding disorder in childhood. ITP is characterized by a low circulating platelet count caused principally by destruction of antibody-coated platelets in the reticuloendothelial system. It can be classified into two major forms, acute and chronic. Acute ITP is usually a benign self-limiting condition with a high probability of spontaneous recovery. Rates of 80% complete remission can be achieved regardless of the treatment. Persistence of thrombocytopenia for more than 6 months defines the chronic form of the disorder, and is seen in approximately 20% of children. Children with chronic ITP also have a good prognosis, with up to 80% remissions over a period of years following diagnosis. The variability of clinical course makes the decision of whether and how to treat difficult. Most children with ITP have mild bleeding symptoms and require no therapy. The commonly used regimens include corticosteroids and intravenous immunoglobulins. So far, there is no evidence that initial therapy can prevent major bleeding or a chronic course of the disease. ITP in childhood remains a disorder with many unsolved questions regarding pathophysiology, diagnostic approach and therapeutic decisions. Large prospective clinical trials with long-term follow-up are needed to define which subgroup of children with ITP should be treated with platelet-enhancing therapy.

Key words: Idiopathic thrombocytopenic purpura, Child.

Introduction

In 1951 William Harrington published the results of his study in which he injected plasma of patients with thrombocytopenic purpura into healthy volunteers (1). They developed a rapid and profound, but transient decrease of platelet counts. Dr. Harrington repeated this experiment on himself as many as 35 times over 2 years. He postulated the presence of an "antiplatelet factor" that subsequently was confirmed as an immunoglobulin (2). Since this human experiment, innumerable articles have been published on idiopathic thrombocytopenic purpura. Although the autoimmune nature of the disease has been appreciated for over 50 years, many aspects of the pathogenesis

have been unanswered and the treatment has remained opportunistic and empirical.

Background

Idiopathic or immune thrombocytopenic purpura (ITP) is the most common acquired bleeding disorder and the most common thrombocytopenia of childhood. The annual incidence is 5 out of 100,000 children (3). ITP is an autoimmune disorder characterized by premature destruction of antibody-sensitized platelets by phagocytic cells in the reticuloendothelial system, mainly in the spleen (4). ITP can be classified based on the duration of the illness into two major forms, acute and chronic. Acute ITP is usually a benign, self-limiting condition presenting in children of either sex between the ages of 2 and 10 years. Often a viral infection or immunization precedes the onset of acute ITP by some days or weeks. Persistence of thrombocytopenia, which is generally defined as a platelet count of less than 150 x 10^9/l, beyond the arbitrary endpoint of 6 months after the initial presentation, defines chronic ITP. Chronic ITP is seen in approximately 20% of children. Factors associated with the development of chronic ITP include age older than 10 years, female gender, and insidious onset. A small number of chronic cases exhibit an intermittent pattern of thrombocytopenia, and are classified as having relapsing or recurrent ITP (5, 6).

Children in whom ITP is diagnosed have an excellent prognosis. Approximately 80% of patients will recover a normal platelet count by 6 months after diagnosis, following pharmacotherapy or observation alone. Even children with the chronic form of the disease have a high potential of spontaneous or drug-induced remission, at a rate of 30 to 80%, which is much higher than in adults (7).

It is also important to distinguish these primary disorders from secondary causes of thrombocytopenia by identification of associated symptoms (Table 1).

Table 1 Secondary causes of ITP in children

Secondary causes of ITP in children
Systemic lupus erythematosus
Immunodeficiency syndromes
Bone marrow failure syndromes
Lymphoproliferative disorders
Myelodysplastic syndromes
Human immunodeficiency virus-associated thrombocytopenia
Drug-induced thrombocytopenia
Alloimmune thrombocytopenia
Congenital/hereditary nonimmune thrombocytopenia

Pathogenesis

Platelets are produced by megakaryocytes in the bone marrow, and have an average life span of 10 days. It was originally thought that platelets were released by shedding from the outer surface of the megakaryocyte, but actually the entire megakaryocyte cytoplasm fragments into platelets, leaving behind a nucleus to be removed by marrow macrophages. Normal marrow contains 6 x 10^6 megakaryocytes per kilogram body weight, with each megakaryocyte releasing up to 1000 platelets. The normal platelet count ranges from 150 to 400 x 10^9/l (8). The spleen continually but transiently sequesters about a third of circulating platelets. Platelets have several growth regulators, including IL-3, IL-6, IL-11, stem cell factor, and erythropoietin. The most important regulatory growth factor is thrombopoietin, a polypeptide that stimulates platelet production following binding to a specific receptor on hematopoietic stem cells, megakaryocytic precursors and megakaryocytes. Thrombopoietin is cleared by binding to its receptor on platelets, and is thought to be produced constitutively (9).

Platelets have a variety of membrane receptors that allow them to interact with different substrates and with each other. The major function of platelets is to maintain primary hemostasis where they lie at the endothelial cell junction, and adhere to the exposed subendothelium of a damaged blood vessel. A platelet count of at least 7 x 10^9/l is necessary to support the vascular integrity. Platelets are involved in every step of the hemostatic process. The essential step of the platelet adherence is the interaction of glycoprotein receptors (GP1b) on the platelet surface with Von Willebrand multimers and exposed collagen microfibrils from the subendothelium. Platelets that have undergone adhesion secrete agonists, thus leading to aggregation of more platelets to form an enlarging platelet plug. With aggregation there is a release of hemostatically active substances from platelet granula, including vasoactive amines, adenine nucleotides, platelet-derived growth factor, beta thromboglobulin, and platelet factor 4. This results in amplification and recruitment of additional platelets, donating their membrane phospholipids for the activation of coagulation factors, thus facilitating thrombin generation and formation of fibrin clot (8, 9).

A key element in the pathogenesis of ITP is loss of self tolerance, leading to the production of autoantibodies against platelet membrane antigens. Children with ITP have polyclonal and monoclonal antibodies with specificity against platelet-specific antigens, in particular glycoproteins IIb/IIIa and Ib/IX (10). These autoantibodies are predominantly IgG, but IgM and IgA types have also been described (11). Reticuloendothelial cells, mainly macrophages found principally in the spleen, bearing receptors for the Fc portion of IgG, clear platelets coated with antibodies from the circulation (12).

For more than 50 years, the only underlying problem in ITP has been recognized as autoimmune platelet destruction, and it was assumed that thrombopoiesis was maximized in response to increased platelet clearance. It has been shown that impaired platelet production also is important in many cases, reflecting the inhibitory effect of platelet antibodies on megakaryopoiesis. Thrombopoietin levels in ITP patients are normal or slightly elevated in contrast to high levels found in thrombocytopenia due to bone marrow failure (9, 12).

The essence of the problem is why children with ITP develop an abnormal immune response. Almost two thirds of the patients have a recent history of viral illness, and it has been postulated that molecular mimicry between viral and self-antigens could initiate autoimmunity. Alternatively, previously suppressed "naturally occurring" autoreactive antibodies might emerge that have escaped natural immune suppression called peripheral tolerance (4). As a part of the platelet destructive process in ITP, cryptic epitopes from platelet antigens are exposed, leading to the formation of new platelet-specific antibodies. It is increasingly apparent that cellular immune mechanisms play a pivotal role in ITP. The production of antiplatelet antibodies by B cells requires antigen-specific T helper (Th)-cells. Ongoing interaction between T cells and B cells is necessary to maintain active platelet autoimmunity. It is also possible that cytotoxic T cells play a role in the destruction of platelets (13, 14).

A number of investigators have studied the pattern of cytokine production in ITP. While there are conflicting reports, most results have shown elevated levels of interleukin-2 and interferon-gamma, favoring prevalence of Th1 subtype cells (12).

Genetic factors have been also proposed to play a role in the development of ITP. Studies have failed to detect linkage to particular HLA genotypes. It has been postulated that polymorphisms in Fcγ receptors of spleen macrophages, leading to functional differences in the ability to bind immuno-

globulin G, may influence the development of ITP (15).

Clinical presentation

The typical presentation of acute ITP is the abrupt onset of skin bleeding in a previously healthy child. There is usually a history of recovery from a recent infectious illness, most often a viral upper respiratory tract infection or gastroenteritis. A seasonal fluctuation, with the peak in the winter and spring months, can be seen. In a minority of cases, ITP follows a specific viral infection, such as Epstein-Barr virus, cytomegalovirus, HIV, rubella, parvovirus, varicella-zoster virus, and hepatitis A, B, C, although there is no correlation between the severity of the viral illness and the degree of thrombocytopenia at presentation. ITP may also be seen following recent immunization with a live virus vaccine, such as the measles, mumps, and rubella vaccine.

More than 95% of patients present with non-palpable hemorrhagic skin lesions (9, 16). Depending on the size, skin hemorrhages are traditionally classified as petechiae (less than 2 mm in the greatest diameter), purpura (2 mm to 1 cm), and ecchymoses (more than 1 cm) (17). In addition to bruising, less than one third of children with ITP present with epistaxis and oral mucosal bleeding. Hematuria, hematochesia, or melena is observed in less than 10 percent of patients. Menometrorrhagia may be seen in adolescent females. Conjunctival and retinal hemorrhages occur infrequently. A slightly palpable spleen is seen in 10 percent of patients.

Although more than half of children with ITP have very low platelet counts, bleeding episodes are less severe than in patients with hypoproductive thrombocytopenia. This finding is consistent with the presence of young, large, hemostatically effective circulating platelets (18). Hence, the physical examination of a child with ITP should be essentially normal aside from evidence of purpuric rash. Malaise, fever, bone or joint pain, remarkable lymphadenopathy, or hepatosplenomegaly are very uncommon findings and should raise strong suspicious of another etiology, such as acute leukemia (5, 12).

Children with ITP usually present between the ages of 2 and 10 years, with a peak incidence at 2 to 5 years. Both sexes are affected equally. Patients who are younger than 2 years or older than 10 years are more likely to develop chronic ITP in combination with some other autoimmune disorder.

Typically, in an untreated child, the bleeding resolves and the platelet count returns to normal in approximately 1 to 3 weeks. About half of the patients achieve a normal platelet count in 4 to 8 weeks, while ITP resolves in two thirds of cases by 3 months. Complete remission, defined as a platelet count greater than 150 x 10^9/l within 6 months of initial diagnosis and without need for ongoing platelet-enhancing therapy, occurs in 80% of patients. This excellent outcome seems independent of any treatment strategy (19, 20).

Chronic ITP includes a small number of children who continue to have persistent thrombocytopenia (platelet count of less than 150 x 10^9/L) beyond 6 months from initial presentation. Although there are no specific predictors for chronic ITP, it occurs more commonly in females aged over 10 years at diagnosis, is usually insidious at onset, and commonly lacking infectious prodroms. Unlike acute ITP, it does not show a seasonal predilection. Children often present with a higher platelet count compared with acute ITP. Most of them are either asymptomatic or present with a history of easy bruising or mucosal bleeding for several months' duration. In this group of patients additional testing should be considered, as secondary causes of thrombocytopenia are more likely (5, 21). Only 10 do 20% of children with acute onset of ITP show a chronic

course according to the definition. Of these, however, over a period of months to many years, 30 to 80% recover completely, regardless of prior treatment (7). According to this observation, chronic ITP in childhood is very rare, and may be subdivided into a mild, therapy-independent form (platelet count > 20 x 10^9/l) and a severe, therapy-dependent form (ongoing bleeding that requires therapy, platelet count usually < 20 x 10^9/l) with an annual incidence of 1 per 2,5 million (22, 23).

The gravest and most feared complication of ITP is intracranial hemorrhage (ICH). Its incidence is fortunately lower than initially thought, and occurs at a rate of 0.1 to 1%. Half of the bleedings occurs in the first 1 to 2 months after initial diagnosis, but are described at any time during the course of the illness, when only a small fraction of the patients are still severely thrombocytopenic. Although the incidence of ICH is extremely low, the mortality rate is significant, with 50% of early occurring hemorrhages being fatal (24). There are no defined ways to predict which patients will develop ICH. Important factors associated with a higher risk of ICH include head trauma, arteriovenous malformation, and use of antiplatelet drugs, such as aspirin, in a child with very low platelet counts (< 10 x 10^9/l). These patients need to be identified early and treated aggressively (25, 26).

Bleeding severity in children with ITP is usually commensurate with the degree of thrombocytopenia, but some patients have minimal or no hemorrhage despite a very low platelet count. Several attempts have been undertaken to establish a scoring system for defining the extent of bleeding in order to standardize therapeutic decisions. Descriptive methods have been employed first. The term "dry" purpura has been used to define cutaneous hemorrhage alone, whereas "wet" purpura signifies active mucous membrane hemorrhage, which is considered susceptible to major bleeding. Bolton-Meggs and Moon arbitrarily divided bleeding signs into four categories: none, mild, moderate, and severe (Table 2) (27). Recently, Buchanan developed a scoring system by measuring signs and symptoms of bleeding on the basis of physical examination and history of new bleeding during the previous 24 hours (Table 3) (28). Bleeding severity is measured on a 5-point scale, and assessed in the skin, from the nose, from the mouth, and globally. The global score encompasses other sites, including menorrhagia, gastrointestinal hemorrhage, and internal bleeding (28, 29).

Table 2 Classification of childhood ITP on the basis of clinical symptoms*

None	No symptoms beyond low platelet count
Mild	Bruising and petechiae
	Occasional minor epistaxis
	Very little or no interference with daily living
Moderate	More severe skin manifestations with some mucosal lesions
Severe	More troublesome epistaxis and menorrhagia
	Bleeding episodes (epistaxis, melena, and/or menorrhagia) requiring hospital admission and/or blood transfusion
	Serious interference with quality of life

*From: Bolton-Maggs PHB, Moon I. Assessment of UK practice for management of acute childhood idiopathic thrombocytopenic purpura against published guidelines. Lancet. 1997;350:620-23.

Table 3 Clinical grading of hemorrhage in childhood ITP based upon history (prior 24 hours) and physical examination*

	Grade 0 (None)	Grade 1 (Minor)	Grade 2 (Mild)	Grade 3 (Moderate)	Grade 4 (Severe)	Grade 5 (Life-threatening or Fatal)
Skin	–	Possibly a few new petechiae and bruises	Definitely new petechiae and bruises	Numerous petechiae and bruises	Extensive petechiae and bruises	–
Epistaxis	–	Blood in nares or on pillow	Active bleeding ≤15 minutes	Active bleeding >15 minutes	Repeated or continuous bleeding	–
Oral	–	Petechiae on palate	Submucosal blood "blisters"; no active bleeding	Intermittent active bleeding	Continuous bleeding	–
Overall	–	Minor or mild skin bleeding; no mucosal hemorrhage	Moderate or severe skin bleeding; no mucosal hemorrhage	Mucosal bleeding not requiring medical attention	Mucosal bleeding or suspected internal hemorrhage requiring medical attention	Documented CNS or life-threatening or fatal hemorrhage in any site

*From: Buchanan GR. Bleeding signs in children with idiopathic thrombocytopenic purpura. J Pediatr Hematol Oncol. 2003;25(Suppl 1):S42-6.

Diagnosis

The diagnosis of childhood ITP is based principally on the exclusion of other causes of thrombocytopenia. Typically, the child with ITP is otherwise healthy, looks well, and presents with spontaneous sudden appearance of purpura and/or bruising. A comprehensive history includes questions regarding recent infections, immunization, use of medications, and personal and family history of bleeding tendency. The physical examination is normal besides purpura. A complete blood count shows isolated thrombocytopenia. Roughly 80% of children present with platelet counts less than 20 x 10^9/l, and often less than 10. Mild anemia with normal red blood cell indices can be seen in as many as 15% of children, indicating a preceding bleeding. The leukocyte count is usually normal, but in some cases may be altered due to concomitant or recent viral or bacterial infection (30). The careful examination of the peripheral blood smear is of utmost importance, excluding the existence of pseudothrombocytopenia caused by platelet clumping, and confirming the normal morphology of all cell lines. Large platelet forms can be seen, particularly when symptoms have been present several days or longer. Coagulation studies are not warranted. Prothrombin time and partial tromboplastin time are invariably normal. Bleeding time, which is a direct test of platelet function, is almost always prolonged but is often shorter than expected for the degree of thrombocytopenia, suggesting that platelet function is normal or increased in many patients with ITP.

In summary, if isolated thrombocytopenia is present and there are no atypical findings that are uncommon in ITP or suggest other etiology, complete blood count and careful film examination by an experienced morphologist should be done, but no further diagnostic tests are indicated. On the other hand, abnormal red blood cell or leukocyte counts or abnormal morphology than cannot be explained easily (e.g. anemia secondary to mucosal bleeding; leucopenia in cases of concomitant viral infection; atypical

lymphocytosis in cases of infectious mononucleosis) should prompt further diagnostic evaluation. The one exception is mild eosinophilia, which is a common finding (9, 12).

Serologic testing for antiplatelet antibodies is not recommended as a part of the routine diagnostic strategy. Although a variety of tests are available, there is as yet no reliable test that has a sufficiently high sensitivity, specificity and reproducibility. Indirect tests that detect free antiplatelet antibodies in the plasma are inferior to direct tests that detect platelet-bound antibodies. Clinicians should be aware that negative test results do not exclude the diagnosis of ITP. Positive test results may lead to inappropriate treatment. Positive testing is described in benign disorders, such as gestational thrombocytopenia, that requires no treatment, or critical disorders, such as thrombotic thrombocytopenic purpura, that requires urgent plasma exchange. Besides, false-positive tests may simply reflect the increased alpha-granule immunoglobulin G present in children (31).

The investigation of proportion of reticulated platelets (young platelets with high RNA content) by fluorescence activated cell sorter (FACS) can help to distinguish between short platelet survival and failure of production, but is not necessary.

Measurement of thrombopoietin plasma levels can be informative in complex cases of thrombocytopenia, and can be useful in distinguishing between reduced production of platelets (high thrombopoietin level) and increased destruction of platelets (normal level). This assay is not recommended as a part of the routine investigation of ITP (32).

Bone marrow aspirate, if performed, typically shows a normal to increased number of megakaryocytes, many of which are immature. An increase in the number of marrow eosinophils and their precursors is present in some cases (33).

It is still a subject of debate whether bone marrow should be examined routinely in children who have suspected ITP. The consensus in the United States, as well as most European countries, is that bone marrow aspiration does not need to be performed in children with a typical clinical presentation and isolated thrombocytopenia, if an observation alone or immunoglobulin therapy has been chosen. The issue of whether bone marrow examination should be done in children before corticosteroid therapy remains still unsolved, but the majority of pediatric hematologists perform a bone marrow aspiration before initiating steroids to exclude the possibility of "masking" acute leukemia. Bone marrow aspirate is necessary in all children with acute ITP and atypical clinical (e.g. hepatosplenomegaly, lymphadenopathy) or laboratory features at diagnosis, as well as in children who fail to achieve any response to initial treatment, or have a chronic course of the disease.

Differential diagnosis

The differential diagnosis of thrombocytopenia in the pediatric population is very broad. Table 4 lists selected causes of thrombocytopenia, and clinical and laboratory features that distinguish them from ITP (9). It is worth emphasizing again that the diagnosis of ITP is based on the presence of an isolated thrombocytopenia in a well-appearing child, and in the absence of atypical clinical and laboratory features.

A complete past medical history and family history is very important. Hereditary thrombocytopenias, including von Willebrand disease type 2B and platelet-type or pseudo-von Willebrand disease may mimic the presentation of ITP, but other family members are often affected, and a larger degree of mucocutaneous bleeding present given a platelet count. History of recurrent infections may lead to the diagnosis of congenital or acquired immunodeficiencies. Thrombocytopenia is a hallmark of Wis-

Table 4 Differential diagnosis of thrombocytopenia in childhood*

Disorder	Clinical features	Laboratory features	Diagnosis confirmation
Immune thrombocytopenic purpura	Petechiae, ecchymoses Rare mucosal bleeding	Thrombocytopenia Rest of CBC normal	By exclusion of other disorders
Drug-induced thrombocytopenia	Petechiae, ecchymoses History of recent exposure to drug	Thrombocytopenia Rest of CBC normal	By measuring drug dependent antibodies When drug withdrawn, thrombocytopenia resolves
Thrombocytopenia absent radius syndrome (TAR)	Diagnosed during infancy Skeletal abnormalities (radial hypoplasia, abnormal thumb)	Thrombocytopenia	Clinical plus laboratory observations
Acquired aplastic anemia	Related to the severity of pancytopenia (e.g. pallor, petechiae, active bleeding)	Generalized pancytopenia	Bone marrow aspiration
Fanconi anemia	Short stature, thumb and other skeletal abnormalities	Other cytopenias may be present. Macrocytes on blood smear	Increased chromosomal fragility when cells exposed to diepoxybutane Genetic analysis
Von Willebrand disease type 2B	Mucosal bleeding Family history of thrombocytopenia	Decreased levels of von Willebrand factor	Ristocetin-induced platelet aggregation Genetic analysis
Bernard – Soulier syndrome	Family history of thrombocytopenia (autosomal recessive)	Mild thrombocytopenia Large platelets	Flow cytometry of platelets (decreased GP Ibα-V-IX complex expression)
Giant platelet syndromes (May – Hegglin, Hermansky – Pudlak, Sebastian)	Family history of thrombocytopenia (autosomal dominant) Renal disease Deafness	Giant platelets (size of red cell) seen on the blood smear Some syndromes include neutrophil inclusions	Electron microscopy of platelets
Wiskott-Aldrich syndrome	Males (X linked) Usually signs of immunodeficiency Recurrent otitis media, eczema	Small platelets seen on smear Low MPV Absent or decreased isohemagglutinins	Abnormal CD43 expression Genetic analysis
Acute leukemia	Usually lymphadenopathy, splenomegaly, hepatomegaly	Other blood counts affected Leukocytosis and anemia	Bone marrow aspiration, cytogenetic analysis
Systemic lupus erythematosus	Usually older children > 10 years Clinical criteria for lupus (e.g. fine hair, rash, joint swelling, etc)	Anemia and leucopenia can be present Elevated ANA, anti-double stranded DNA	Clinical plus laboratory data
Hemolytic uremic syndrome	History of bloody diarrhea Acute renal failure	Elevated BUN and creatinine Schistocytes on blood smear Escherichia coli 0157:H7 in stool	Clinical plus laboratory data

*From: Di Paola JA, Buchanan GR. **Immune thrombocytopenic purpura. Pediatr Clin N Am. 2002;49:911-28.**

kott-Aldrich syndrome, but has associated features of eczema, recurrent infections, and a propensity to develop autoimmune disorders. It usually presents in the first months of life, and there is a predisposition to significant bleeding out of proportion to the degree of thrombocytopenia. Congenital amegakaryocytic thrombocytopenia is a bone marrow failure syndrome that presents with severe thrombocytopenia in the neonatal period. HIV-associated thrombocytopenia should be considered in a child with a family or transfusion history compatible with this diagnosis. Drug-induced thrombocytopenia is uncommon, but can occur in children who have had a recent illness and have completed or are completing a course of medications such as penicillin, sulphonamides, or quinidine.

Besides a history, it is essential to make a thorough physical examination of a child with thrombocytopenia. Special attention should be given to the presence of skeletal malformations or short statue, which is found in patients with Fanconi anemia and thrombocytopenia-absent radii syndrome. Cutaneous rash and joint swelling might be suspicious of a more severe autoimmune disorder like systemic lupus erythematosus that affects usually children older than 10 years. The presence of hepatosplenomegaly, lymphadenopathy, or bone pain in an ill-appearing child is a characteristic of hematological malignancies.

Finally, a careful assessment of a peripheral blood smear by an experienced hematologist cannot be overemphasized. In inherited thrombocytopenias platelet morphology and platelet size are very useful in making the proper diagnosis. Bernard-Soulier syndrome is characterized by abnormal large platelets and a significant degree of bleeding. May-Hegglin anomaly is another syndrome associated with giant platelets and variable thrombocytopenia. One of its distinguishing features is large inclusions in granulocytes and monocytes known as Dohle bodies. Thrombocytopenic purpura and hemolytic uremic syndrome are characterized by thrombocytopenia, microangiopathic hemolysis, and organ dysfunction. The blood smear reveals fragmented cells, schistocytes, and microspherocytes. The presence of blast cells indicates hematological malignancy and should prompt bone marrow aspiration (9, 34).

Treatment

There is a consensus that childhood acute ITP is generally a short benign self-limited disorder that, in the majority of cases, requires minimal or no therapy. The natural history of the disease is that 80% of cases recover within a few months of presentation with or without therapy. It is recognized that drug therapy does not alter the clinical course of the disease but may shorten the period of profound thrombocytopenia. Therefore intervention, if any, should be directed at early control of active bleeding. Standard supportive care that is important in the management of a child with very low platelet counts includes avoidance of medications with antiplatelet or anticoagulant activity. If possible, the child's physical activity should be limited as long as the platelet count is less than 20 x 10^9/L, there is an excessive bruising or new petechiae, or both. Contact sports should be avoided while the platelet count is less than 50 x 10^9/l. In active young children with marked thrombocytopenia, where limiting their activities is not feasible, protective headgear may be helpful, as well as for toddlers lining their crib with protective padding.

Pharmacotherapy or observation only of a child with acute ITP has been discussed for years, and has divided pediatric hematologists between so called interventionists and non-interventionists (5, 35). Interventionists advocate the use of drug therapy in all children with very low platelet counts to prevent severe bleeding. Non-interventionists follow the "watchful waiting" method,

involving careful observation and reassurance of the patient and parents, and arguing that therapy, often causing undesirable side effects, has not proven to prevent intracranial hemorrhage. Several different guidelines for the diagnosis and management of ITP in all age groups have been published, and are still a subject of debate. The American Society of Hematology (ASH) practice guidelines recommend that children with ITP and platelet counts less than 20 x 10^9/l and significant mucosal bleeding, or those with platelet counts less than 10 x 10^9/l and minor purpura, be treated with specific regimens of IVIG or oral prednisone (36). By contrast, recommendations from the British Paediatric Haematology Working Group state that treatment of children with ITP should be decided on the basis of clinical symptoms, not on the platelet count alone. Pharmacotherapy is reserved for children who have an overt hemorrhage and the platelet count less than 20 x 10^9/l, or those who have an organ- or life-threatening bleeding irrespective of the platelet count (37).

Despite existing guidelines, the decision of when to treat, what treatment to use and the need for hospitalization is based more on opinion than evidence. Initial treatment options for childhood ITP include steroids, intravenous immunoglobulin, and, for children who are Rh positive, anti-Rh immunoglobulin ("anti-D").

Steroids. Oral corticosteroids have been used for many years for the treatment of ITP in all age groups. They are presumed to act through several mechanisms, including inhibition of reticuloendothelial system phagocytosis of antibody-coated platelets, inhibition of synthesis of antiplatelet antibodies, improved platelet production, and increased microvascular endothelial stability. A variety of dosage regimens have been reported. The traditional regimen is prednisone at 2 mg/kg/day (60 mg maximum) for 14 days with subsequent tapering, discontinuing by day 21. A regimen of 4 mg/kg/day for 7 days, then tapered to day 21 is equally effective. An alternative to these regimens is pulse therapy: dexamethasone 20-40 mg/m^2 (40 mg maximum) for 4 consecutive days, or megadose pulse therapy with methylprednisolone at a dose of 30 mg/kg/day intravenously or orally (1g maximum) for 3 consecutive days. More recently a regimen of prednisone at a dose of 4 mg/kg/day orally for 4 days with no tapering has been shown to be more effective than the conventional standard dose, and may be less toxic than high-dose steroids. Although inexpensive and easy to administer, steroids may be associated with considerable side effects, including weight gain, fluid retention, cushingoid facies, acne, hyperglycemia, hypertension, moodiness, pseudotumor cerebri, cataracts, osteoporosis, avascular necrosis, and immunosuppression with a risk of infection. Toxicity is related to the dose and duration of therapy (5, 9).

Intravenous immunoglobulin. Imbach and colleagues first reported the successful use of intravenous immunoglobulin (IVIG) in the management of acute ITP in a small series of children (38). The effect of IVIG is caused by a competitive inhibition of Fc receptors on phagocytes of the reticuloendothelial system, allowing antibody-coated platelets to circulate. The traditional dose of IVIG is 2 g/kg divided over 2 to 5 days. It has been shown that a single dose of 0.8 g/kg of IVIG has as favorable result as higher doses, and has remained a gold standard for a rapid increase of platelets in children who require treatment. Although more costly than steroids, IVIG is favored by many clinicians as a primary treatment for patients with ITP. Randomized trials have shown that periodic treatment with IVIG increases platelet count more rapidly than treatment with standard doses of prednisone. The yields of platelet recovery, however, are not significantly different from those with higher doses of prednisone. The adverse effects of IVIG are common but

generally mild, occurring in 15 to 75% of patients. They include flu-like symptoms such as headache, nausea, lightheadedness, and fever. Occasionally aseptic meningitis, anaphylaxis, hemolytic anemia, hepatitis C transmission, and hemiplegia are seen (5, 9).

Table 5 Commonly used regimes for treatment of acute ITP in children*

Corticosteroids	Dose
Prednis(ol)one oral	1-2 mg/kg/d for 21 days (maximum dose, 60 mg/d) 4 mg/kg/d for 4 days with abrupt discontinuation (maximum dose, 180 mg/d)
Methylprednis(ol)one oral or i.v.	10-30 mg/kg/d for several days
Dexamethasone oral pulse	20-40 mg/m^2 for 4 consecutive days (every month, 6 cycles)
Immunoglobulins	**Dose**
IVIgG	0.4 g/kg/d for 5 days 1 g/kg/d for 2 days 0.8 g/kg/d once 0.25 to 0.5 g/kg/d for 2 days or once
Anti-D	25 µg/kg/d for 2 days 40-50 µg/kg/d once 75 µg or more /kg/d once

*From: Gadner H. Management of immune thrombocytopenic purpura in children. Rev Clin Exp Hematol. 2001;5:201-221.

Anti-D immunoglobulin. Anti-D is a plasma-derived immunoglobulin prepared from donors with high titers of anti-Rh (D) antibodies. Anti-D can effectively raise the platelet count by blockage of the reticuloendothelial system with antibody-coated red blood cells, thereby minimizing removal of antibody-coated platelets. The patients must be Rh(D)-positive and must have a functioning spleen. Although the optimal dose for anti-D has not been established, the generally recommended dose is 50 to 75 µg/kg as a short intravenous infusion. Responses to anti-D therapy are comparable in magnitude and duration with those observed after IVIG therapy. Anti-D is well-tolerated with only minimal side effects reported in 3% of infusion, including headache, nausea, chills, fever, and dizziness. Hemolytic anemia is the main adverse and inevitable reaction of anti-D, owing to the binding of anti-D antibody to Rh(D)-positive red blood cells. The average decline in hemoglobin concentration ranges from 0.5 to 1 g/dl, and in far the most instances does not require medical intervention.

The most commonly used regimens of steroids, IVIG and anti-D for the initial treatment of acute ITP in children are listed in Table 5. The comparison of these treatment approaches is summarized in Table 6.

Table 6 Comparison of various treatment regimes in children with ITP*

Treatment Response	Prednisone (4 mg/kg/day, d 1–7, max 60 mg)	IV Immunoglobulin (1–2 g/kg)	Anti-D Immunoglobulin (75 µg/kg)
Response > 20.000 at 48 hours	60–70% of patients	70–80% of patients	77% of patients
Common side effects	Weight gain, irritability, hypertension, stomach pain, hyperglycemia	Post-infusion headache, vomiting, allergic reactions, fever, chills	Hemolysis, chills, fever, headache
Rare but severe reactions	Gastric ulcer, reflux, bleeding, hypertension-induced intracranial hemorrhage	Anaphylaxis, aseptic meningitis, renal failure	Massive hemolysis with associated back pain, myalgia, anemia
Duration of initial response (days)	Wide range of response after 30 days of weaning from initial dose to 0	21–72 days with platelet counts greater than 20,000/mm^3	21–48 days based on the 75 µg/kg dose

*From: Nugent DJ. Immune thrombocytopenic purpura of childhood. Hematology Am Soc Hematol Educ Program. 2006:97-103.

On very rare occasions, children with acute ITP and severe thrombocytopenia present with life-threatening bleeding. Management of such cases is challenging and involves measures that have the potential to increase the circulating platelet count rapidly. Appropriate interventions include immediate intravenous administration of methylprednisolone at a dose of 30 mg/kg (maximum dose 1 g) over 30 minutes plus massive (two- to threefold larger than usual) transfusions of donor platelets in an attempt to boost the circulating platelet count temporarily. After administration of methylprednisolone and platelets, an infusion of IVIG at a dose of 1 g/kg should be started, with IVIG and methylprednisolone repeated daily as clinically indicated, usually for 2 or 3 days. Life-threatening hemorrhage is the only indication for platelet transfusion in ITP. The aim of these measures is to maintain platelet counts greater than 50 x 10^9/l. Emergency splenectomy may be considered in individual patients who fail to increase platelet counts or stop bleeding (39, 40). Reports with recombinant factor VIIa are limited but this hemostatic agent should be considered in critical situations (41).

Chronic ITP may present with variable symptoms and platelet counts. In up to 80% of these patients spontaneous remission will occur months or years later. Many children are symptomless and have platelet counts in the range of 20 to 100 x 10^9/l, thus requiring no treatment. Some cases may occasionally need platelet-enhancing therapy, for which the least toxic approach should be chosen. The smallest but most important category is children who have platelet counts less than 20 x 10^9/l and bleeding symptoms (41). In this subgroup second-line therapies or splenectomy may need to be considered. Pharmacotherapy options include short courses or pulses of corticosteroids, or intermittent IVIG or anti-D. The goal of these repetitive treatments is to maintain a hemostatically safe platelet count (5). The novel therapeutic agent is rituximab, a human murine (chimeric) anti-CD20 monoclonal antibody that induces selective depletion of B-lymphocytes necessary for antiplatelet antibody production (42, 43).

Splenectomy should be considered in children with chronic ITP, who fail to respond to drug therapy and have persistent significant bleeding problems and platelet counts usually less than 10 x 10^9/l (44). These conservative guidelines reflect the high rate of remissions that occur in children who have early chronic ITP, and the small but definite risk of overwhelming postsplenectomy sepsis, especially in children under 5 years of age. As the spleen is both a major site of platelet destruction and antiplatelet antibody production, splenectomy may induce sustained remission in the large majority of patients (60 to 90%). When possible, surgery should be performed using laparoscopic techniques. Presplenectomy immunizations and subsequent long-term penicillin prophylaxis is necessary (5, 45).

Children with chronic and severe ITP who fail to remit after splenectomy present very challenging management decisions for pediatric hematologists. No specific therapy recommendations exist for this small group of patients. An array of agents, which have been used primarily in adults, is available (46). They include azathioprine, cyclophosphamide, vinca alkaloids, combination chemotherapy, danazol, cyclosporine A, dapsone, colchicine, and interferon-alpha (47, 48). Thrombopoietin and thrombopoietin-like agents are novel promising thrombopoiesis-stimulating agents (49). The true place of all these approaches in the management of children with chronic refractory ITP remains to be determined through prospective clinical trials.

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