

# Childhood Immune Thrombocytopenic Purpura: Diagnosis and Management

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Immune thrombocytopenic purpura (ITP) is an autoimmune disorder characterized by a low circulating platelet count caused by destruction of antibody-sensitized platelets in the reticuloendothelial system [1]. ITP can be classified based on patient age (childhood versus adult), duration of illness (acute versus chronic), and presence of an underlying disorder (primary versus secondary). Persistence of thrombocytopenia, generally defined as a platelet count of less than  $150 \times 10^9/L$  for longer than 6 months, defines the chronic form of the disorder. Secondary causes of ITP include collagen vascular disorders, such as systemic lupus erythematosus (SLE); immune deficiencies, such as common variable immunodeficiency (CVID); and some chronic infections (eg, HIV and hepatitis C).

This article focuses on the diagnosis and management of children (under 18 years of age) who have acute and chronic ITP. Emphasis is placed on areas of controversy and new therapies.

## Pathophysiology

The pathophysiology of ITP increasingly is understood better (reviewed by Cines and Blanchette [1]). Not surprisingly, it is complex with involvement of many players in the human immune orchestra, including antibodies, cytokines, antigen-presenting cells, costimulatory molecules, and T and B lymphocytes (including T-helper, T-cytotoxic, and T-regulatory lymphocytes). Current knowledge is summarized later.

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A key element in the pathophysiology of ITP is loss of self tolerance leading to the production of autoantibodies directed against platelet antigens. Evidence for an “antiplatelet factor” in the plasma of subjects who have ITP was provided in a seminal report from Harrington and coworkers [2] in 1951. The investigators demonstrated that the infusion of plasma from subjects who had ITP into volunteers induced a rapid fall in platelet count and a clinical picture that mimics ITP. The “antiplatelet factor” subsequently was confirmed as an immunoglobulin [3]. Now it is known that the autoantibodies in patients who have ITP mostly are of the IgG class with specificity against platelet-specific antigens, in particular, glycoproteins IIb/IIIa and Ib/IX. Unfortunately, accurate detection of platelet autoantibodies is difficult and not available routinely in most clinical hematology laboratories; clinicians should be aware that indirect platelet autoantibody tests (tests that detect free autoantibodies in the plasma) are inferior to direct tests (tests that detect platelet-bound autoantibodies) and that even with the best direct tests performed in expert immunohematology laboratories, the positivity rate in patients who have well-characterized ITP does not exceed 80% [4]. A negative platelet antibody test, therefore, does not exclude a diagnosis of ITP. For this reason, platelet antibody testing is not recommended as part of the routine diagnostic strategy [5].

It is increasingly clear that cellular immune mechanisms play a pivotal role in ITP [1]. The production of antiplatelet antibodies by B cells requires antigen-specific, CD4-positive, T-cell help (Fig. 1). It also is possible that in some ITP cases, cytotoxic T cells play a role in the destruction of platelets. A possible sequence of events in ITP is as follows. A trigger, possibly an infection or toxin, leads to the formation of antibodies/immune complexes that attach to platelets. Antibody-coated platelets then bind to antigen-presenting cells (macrophages or dendritic cells) through low-affinity Fc $\gamma$  receptors (Fc $\gamma$  RIIA/Fc $\gamma$  RIIIA) and are internalized and degraded. Activated antigen-presenting cells then expose novel peptides on the cell surface and with costimulatory help facilitate the proliferation of platelet antigen-specific, CD4-positive, T-cell clones. These T-cell clones drive autoantibody production by platelet antigen-specific B-cell clones. As part of the platelet destructive process in ITP, cryptic epitopes from platelet antigens are exposed, leading to the formation of secondary platelet antigen-specific T-cell clones, with stimulation of new platelet antigen-specific B-cell clones and broadening of the immune response. The autoantibody profile of individual patients who have ITP reflects activity of polyclonal autoreactive B-cell clones derived by antigen-driven affinity selection and somatic mutation.

Although increased platelet destruction clearly plays a key role in the pathogenesis of ITP, it is now recognized that impaired platelet production also is important in many cases. In adults, as many as 40% of ITP cases may have reduced platelet turnover, reflecting the inhibitory effect of platelet autoantibodies on megakaryopoiesis [6]. Studies of platelet kinetics in

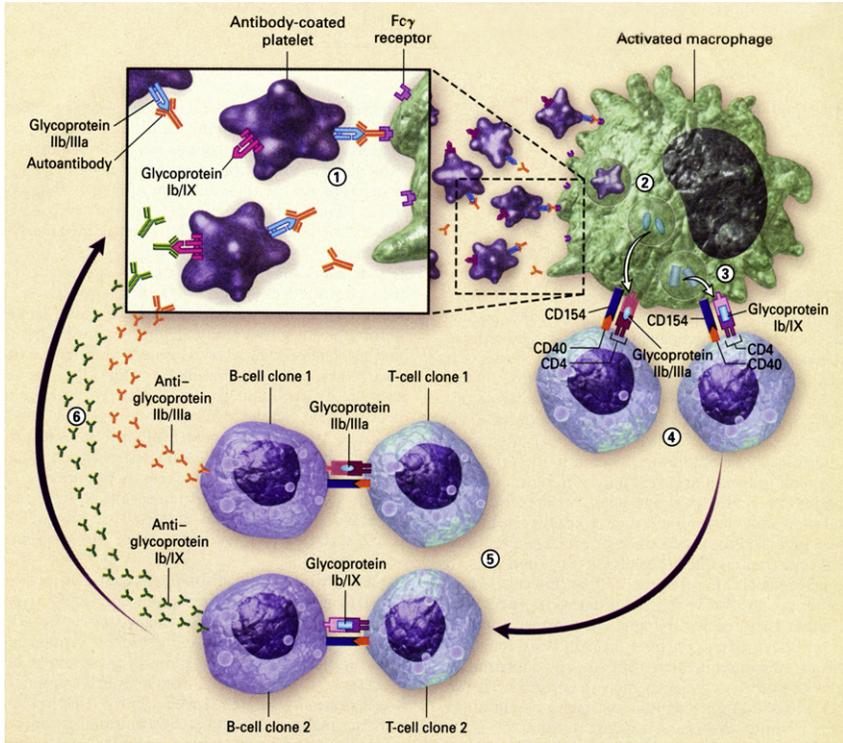


Fig. 1. Pathogenesis of epitope spread in ITP. The factors that initiate autoantibody production are unknown. Most patients have antibodies against several platelet-surface glycoproteins at the time the disease becomes clinically evident. Here, glycoprotein IIb/IIIa is recognized by autoantibody (orange, inset), whereas antibodies that recognize the glycoprotein Ib/IX complex have not been generated at this stage (1). Antibody-coated platelets bind to antigen-presenting cells (macrophages or dendritic cells) through Fc $\gamma$  receptors and then are internalized and degraded (2). Antigen-presenting cells not only degrade glycoprotein IIb/IIIa (light blue oval), thereby amplifying the initial immune response, but also may generate cryptic epitopes from other platelet glycoproteins (light blue cylinder) (3). Activated antigen-presenting cells (4) express these novel peptides on the cell surface along with costimulatory help (represented in part by the interaction between CD154 and CD40) and the relevant cytokines that facilitate the proliferation of the initiating CD4-positive T-cell clones (T-cell clone 1) and those with additional specificities (T-cell clone 2) (5). B-cell immunoglobulin receptors that recognize additional platelet antigens (B-cell clone 2) thereby also are induced to proliferate and synthesize antiglycoprotein Ib/IX antibodies (green) in addition to amplifying the production of anti-glycoprotein IIb/IIIa antibodies (orange) by B-cell clone 1 (6). (From Cines DB, Blanchette VS. Immune thrombocytopenic purpura. *N Engl J Med* 2002;346:995–1008; with permission. Copyright © 2002, Massachusetts Medical Society. All rights reserved.)

children who have ITP are limited but it is possible that a similar situation exists. There also is evidence that platelet autoantibodies may induce thrombocytopenia by inhibiting proplatelet formation [7]. Circulating thrombopoietin (TPO) levels in patients who have ITP typically are normal or increased only slightly, reflecting the normal or only slightly reduced TPO

receptor mass in this acquired platelet disorder. In contrast, TPO levels are high in inherited platelet production disorders, such as thrombocytopenia-absent radii or congenital amegakaryocytic thrombocytopenia [8]. TPO testing generally is not available, but these observations have led to the question of whether or not TPO or molecules mimicking TPO may increase platelet production and be a new treatment strategy in ITP. Several such agents currently are in clinical trials.

### Differential diagnosis

Primary ITP is a diagnosis of exclusion. The question, “When does a low platelet count not mean ITP?” is important, especially for atypical cases. When an unexpected low platelet count in a child is obtained, artifact or laboratory error should be considered first and excluded. Pseudothrombocytopenia is an example of spurious thrombocytopenia that is caused by platelet aggregation and clumping in the presence of ethylenediamine tetraacetic acid (EDTA) anticoagulant [9]. Examination of well-stained blood smears prepared from a venous blood sample collected separately into EDTA and 3.8% sodium citrate anticoagulant usually confirms or excludes pseudothrombocytopenia. A smear prepared from the collection tube with EDTA should demonstrate platelet clumping, whereas a smear prepared from the tube with sodium citrate should not. Some patients, however, have platelets that also clump in citrate anticoagulant.

A detailed history, careful physical examination, and results of selected tests confirm or eliminate common causes of secondary thrombocytopenia, such as SLE. A positive antinuclear antibody is common in children who have ITP and, as an isolated finding, does not confirm or exclude SLE [10]; more specific tests, such as an anti-double-stranded DNA test, should be ordered if a diagnosis of SLE-associated ITP is suspected. A transfusion history should be obtained in all cases and, depending on the age of the child, the history should include questioning about drug use (prescription and nonprescription) and sexual activity. If relevant, testing for antibodies to hepatitis C and HIV should be performed.

A detailed family history should be obtained in all cases. Especially in children who have apparent “chronic” ITP and isolated moderate thrombocytopenia, the possibility of an inherited thrombocytopenia should be considered. The topic, “inherited thrombocytopenia: when a low platelet count does not mean ITP,” is the focus of an excellent review [11]. The inherited thrombocytopenias can be classified based on platelet size (large, normal, and small) and gene mutations. They include conditions, such as the MYH9-related macrothrombocytopenias, Wiskott-Aldrich syndrome (WAS), and rare conditions, such as gray platelet syndrome (Box 1). The pattern of inheritance (eg, X-linked in boys who have WAS) and abnormalities on peripheral blood smear (eg, Döhle-like inclusions in neutrophils of patients who have MYH9 disorders or pale agranular platelets in gray platelet syndrome) may provide

**Box 1. Inherited thrombocytopenias classified by platelet size***Small platelets [MPV < 7 fL]*

WAS

X-linked thrombocytopenia

*Normal-sized platelets [MPV 7–11 fL]*

Thrombocytopenia-absent radii

Congenital amegakaryocytic thrombocytopenia

Radioulnar synostosis and amegakaryocytic thrombocytopenia

Familial platelet disorder with associated myeloid malignancy

*Large/giant platelets [MPV > 11 fL]*MYH9<sup>a</sup> syndromes

- May-Hegglin anomaly
- Fechtner syndrome
- Epstein syndrome
- Sebastian syndrome

Mediterranean thrombocytopenia

Bernard-Soulier syndrome

Velocardiofacial/DiGeorge syndrome

Paris-Trousseau thrombocytopenia/Jacobsen syndrome

Gray platelet syndrome

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*Abbreviation:* MPV, mean platelet volume.

<sup>a</sup> MYH9 gene encodes for the nonmuscle myosin heavy-chain IIA.

*Data from* Drachman JG. Inherited thrombocytopenia: when a low platelet count does not mean ITP. *Blood* 2004;103:390–8.

important clues to the underlying disorder. Failure of patients who have apparent “chronic ITP” and moderate thrombocytopenia to respond to front-line platelet-enhancing therapies, such as high-dose intravenous (IV) immunoglobulin G (IVIg) or IV anti-D, should prompt consideration of an alternate diagnosis. Additional investigation in such cases should include screening for type 2B von Willebrand disease, pseudo-von Willebrand disease, and Bernard-Soulier syndrome. In males who have small platelets, WAS or X-linked thrombocytopenia should be considered. These latter conditions can be confirmed by screening for mutations in the WASP gene. Boys who have WASP gene mutations may have significant immunologic abnormalities.

**Childhood acute immune thrombocytopenic purpura***Clinical and laboratory features*

Thrombocytopenia for less than 6 months defines the entity acute ITP. Typically, children who have acute ITP are young, of previous good health,

and present with sudden onset of bruising or a petechial rash. In a series of 2031 children who had newly diagnosed ITP, reported by Kühne and colleagues [12] in 2001 for the Intercontinental Childhood ITP Study Group (ICIS), the mean age at presentation was 5.7 years. Approximately 70% of the cohort were children ages 1 to 10 years with 10% of the cohort infants (older than 3 and less than 12 months old) and the remainder 20% older children (ages 10 to 16 years) [13]. Male and female children were affected approximately equally with the caveat that boys outnumbered girls in young children, especially those less than 1 year of age (Fig. 2) [12]. The predominance of boys who had ITP in children under 10 years of age is reported in several other studies [14–16]. In approximately two thirds of cases, the onset of acute ITP is preceded by an infectious illness, most often an upper respiratory tract infection; in a minority of cases, ITP follows a specific viral illness (rubella, varicella, mumps, rubeola, or infectious mononucleosis) or immunization with a live virus vaccine [17,18]. The risk for ITP after mumps-measles-rubella vaccine is estimated at approximately 1 in 25,000 doses [19]. In children who have acute ITP, the interval between the preceding infection and the onset of purpura varies from a few days to several weeks, with the most frequent interval approximately 2 weeks [20]. Physical examination at presentation is remarkable only for the cutaneous manifestations of severe thrombocytopenia with bruising or a petechial rash present in almost all cases (Table 1). Clinically significant lymphadenopathy or marked hepatosplenomegaly are atypical features; however, shotty cervical adenopathy is common in young children and a spleen tip may be palpable in 5% to 10% of cases [20,21]. Epistaxis (often minor, sometimes severe) is a presenting symptom in approximately one quarter of affected children; hematuria occurs less frequently [20].

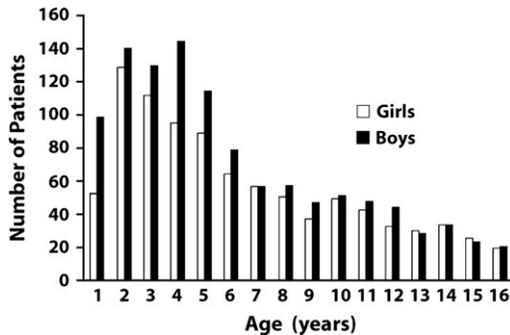


Fig. 2. Age (years) of children who had newly diagnosed ITP entered into the Intercontinental Childhood ITP Registry. (From Kühne T, Imbach P, Bolton-Maggs PHB, et al. Newly diagnosed idiopathic thrombocytopenic purpura in childhood: an observational study. *Lancet* 2001;358:2122–25; with permission.)

Table 1  
Presenting features in children who have acute immune thrombocytopenic purpura

Investigator	Number of cases	Male:female ratio	Preceding infectious illness	Hemorrhagic manifestations		
				Purpura/petechiae	Epistaxis	Hematuria
Choi (1950–1964) <sup>a</sup> [20]	239	117:122	119/239	235/239	76/239	20/239
Lusher (1956–1964) [21]	152	69:83	122/146	—	46/152	8/152
Blanchette (1974–1982) [22]	80	37:43	58/80	75/80	20/80	3/80
Bolton-Maggs (1995–1996) [14]	427	213:214	245/427	310/427	85/427	6/427
Total	898	436:462	544/892 (60.9%)	620/746 (83.1%)	227/898 (25.3%)	37/898 (4.1%)

<sup>a</sup> Years in parenthesis represent the period of observation.

The key laboratory finding in children who have acute ITP is isolated, and often severe, thrombocytopenia. In more than half of cases, platelet counts at presentation are less than  $20 \times 10^9/L$  (Fig. 3). Other hematologic abnormalities are consistent with a diagnosis of childhood acute ITP only if they can be explained easily (eg, anemia secondary to epistaxis/

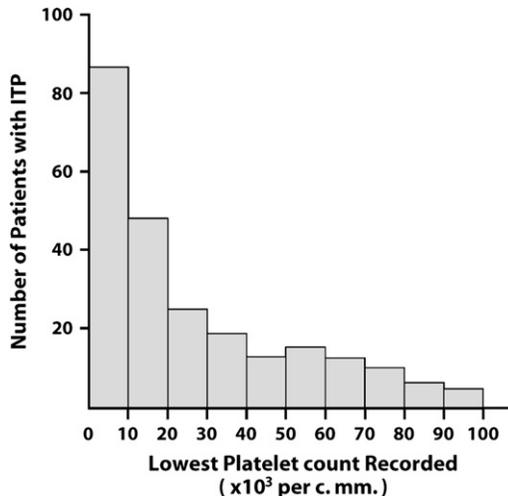


Fig. 3. Lowest platelet count observed in children who had ITP. (From Choi SI, McClure PD. Idiopathic thrombocytopenic purpura in childhood. *Can Med Assoc J* 1967;97:562–8; with permission. Copyright © 1967, Canadian Medical Association.)

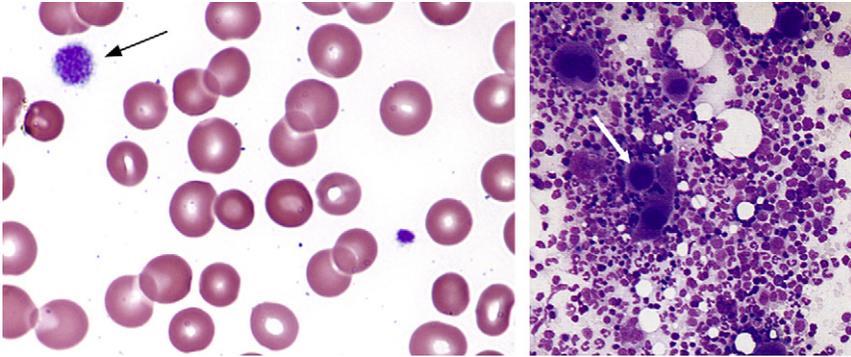


Fig. 4. Blood smear and bone marrow aspirate from a child who had ITP showing large platelets (blood smear [left]) and increased numbers of megakaryocytes, many of which appear immature (bone marrow aspirate [right]).

menorrhagia) or atypical lymphocytosis in cases of infectious mononucleosis. The one exception is mild eosinophilia, which is a common finding [21]. The blood smear shows a marked decrease in platelets with some platelets that are large (megathrombocytes) (Fig. 4). A bone marrow aspirate, if performed, typically shows normal to increased numbers of megakaryocytes, many of which are immature (see Fig. 4). An increase in the number of bone marrow eosinophil precursors is present in some cases.

#### *Natural history of childhood acute immune thrombocytopenic purpura*

The natural history of childhood acute ITP is well documented (reviewed by Blanchette and Carcao [22]). Complete remission, defined as a platelet count greater than  $150 \times 10^9/L$  within 6 months of initial diagnosis and without the need for ongoing platelet-enhancing therapy, occurs in at least two thirds of cases. This excellent outcome seems independent of any management strategy. As an example, in the prospective study reported by Kühne and colleagues [12], complete remission rates of 68%, 73%, and 66% were reported in children who received no treatment, IVIG, or corticosteroids, respectively. These data are similar to the 76% complete remission rate reported by George and colleagues [5] on the basis of a review of 12 case series involving 1597 cases. A recent study of children from five Nordic studies described a simple clinical score that predicts early remission [23]. If confirmed, this could identify those children who might be left without active therapy for low platelet counts. Predictors of early remission were abrupt onset of illness, preceding infection, male gender, age under 10 years, wet purpura, and a platelet count less than  $5 \times 10^9/L$ .

The outcome for children who have acute ITP who continue to manifest thrombocytopenia beyond 6 months from initial presentation generally is good. Published reports suggest that as many as one third of such children have spontaneous remission of their illness from a few months to several

years after initial diagnosis [5,24]. In one study, 61% was predicted at 15 years of follow-up [25]. Most spontaneous remissions occur early, and the number of children who have severe thrombocytopenia (platelet counts  $<20 \times 10^9/L$ ) and who are symptomatic with bleeding symptoms and, therefore, are therapy dependent more than 1 year after initial diagnosis is small. In a Swiss-Canadian retrospective analysis of 554 children who had newly diagnosed ITP and platelet counts less than  $20 \times 10^9/L$ , the percentages of children who had platelet counts less than  $20 \times 10^9/L$  at 6, 12, 18, and 24 months after diagnosis were 9%, 6%, 4%, and 3%, respectively (Fig. 5) [26]. This is the small subgroup of children for whom splenectomy ultimately may need to be considered.

The case for treatment of children who have acute ITP relates to those who have significant bleeding and consideration of the very small, but finite, risk for intracranial hemorrhage (ICH). The risk of this feared complication was 0.9% in a series of 1693 children reviewed by George and colleagues [5]. This figure, however, probably is an overestimate reflecting that reports in the literature mainly are from academic centers that likely are referred the most severe cases. Based on data in the United Kingdom, Lilleyman has estimated an incidence of 0.2% of ICH in children who have newly diagnosed ITP [27], a figure consistent with the 0.17% incidence rate (3 of 1742 children who had newly diagnosed acute ITP) reported by Kühne and colleagues [13] on behalf of the ICIS.

Whatever the true incidence of ICH in children who have acute ITP, there is no doubt that this event is a devastating and sometimes fatal complication in this generally benign childhood disorder. The percent of cases of ICH occurring within 4 weeks of initial diagnosis varied from 19% to 50%

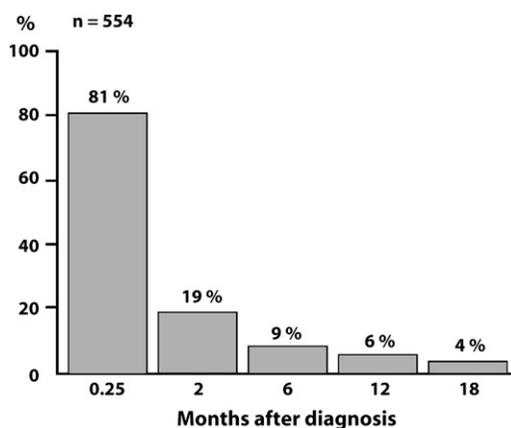


Fig. 5. Percentage of children ( $n = 554$ ) who had ITP and platelet counts below  $20 \times 10^9/L$  at 1 week, 2, 6, 12, and 18 months after diagnosis of acute ITP. Swiss-Canadian retrospective analysis. (From Imbach P, Akatsuka J, Blanchette V, et al. Immunthrombocytopenic purpura as a model for pathogenesis and treatment of autoimmunity. *Eur J Pediatr* 1995;154(Suppl 3): S60-4; with permission.)

in different reports [5,27,28]; in one retrospective review, 10% (7/69) of cases of ICH occurred within 3 days of diagnosis of ITP [29]. Trauma to the head and use of antiplatelet drugs, such as aspirin, were identified as risk factors for ICH in children who had ITP and very low platelet counts [30].

Unfortunately, a prospective randomized controlled trial to determine definitively whether or not therapeutic intervention can decrease the incidence of ICH significantly in children who have newly diagnosed ITP and platelet counts below  $20 \times 10^9/L$  is not feasible, because of the large numbers of cases required to ensure a statistically significant outcome. Physicians who care for children who have acute ITP, therefore, must act in the best interest of each child without the benefit of definitive data. Because of the significant morbidity and mortality associated with ICH and the availability of highly effective platelet-enhancing therapies, some recommend that families of young children who have newly diagnosed acute ITP at risk for ICH (who have platelet counts  $<10 \times 10^9/L$ ) be offered the option of treatment using the minimum therapy necessary to increase the platelet count rapidly to a safe, hemostatic level. There is no current evidence, however, that such a management strategy significantly reduces the incidence of ICH in children who have ITP, although intuitively this seems probable.

In addition, there is evidence to suggest that the rate of platelet response to frontline therapies (corticosteroids or IVIG) in the subset of children who have ITP and clinically significant hemorrhage is suboptimal [31]. Discussion with parents and children, if of appropriate age, should include consideration of best available evidence with regard to the three key issues: (1) to treat or not to treat (2) to perform a bone marrow aspirate or not and (3) to hospitalize or not.

## **To treat or not to treat**

### *Observation*

The case for observation of children who have acute ITP rests with the knowledge that acute ITP is, for the majority of affected children, a benign self-limiting disorder, usually with mild clinical symptoms and has a low risk for serious bleeding (approximately 3% with ICH being rare) and the fact that there are no prospective studies that clearly indicate a decrease in the incidence of ICH associated with treatment [32]. Several children who had ITP-associated ICH were receiving platelet-enhancing therapy at the time of the hemorrhage [28]. In addition, all treatments suffer from the disadvantage of side effects, which can be severe.

Guidelines for initial management of children who have acute ITP have been published and reflect the ongoing debate, “to treat or not to treat” [5,33–36]. Recommendations from the Working Party of the British Committee for Standards in Haematology General Haematology Task Force

state that treatment of children who have acute ITP should be decided on the basis of clinical symptoms in addition to cutaneous signs, not the platelet count alone [36]. The Working Party considered it appropriate to manage children who have acute ITP and mild clinical disease expectantly, with supportive advice, and a 24-hour contact point irrespective of the platelet count. Based on these guidelines, intervention is reserved for the few children who have overt hemorrhage and platelet counts below  $20 \times 10^9/L$  or those who have organ- or life-threatening bleeding irrespective of the circulating platelet count [34,36]. Many clinicians in Europe manage children who have ITP expectantly (ie, without medication to increase the platelet count) because of the rapid remissions in most cases, the low risk for bleeding, and toxicities of currently available medical therapies. Data are reported from the United Kingdom and Germany promoting the use of advice and support to children and their families during the usually short duration of the illness [15,32,37].

### *Corticosteroids*

The corticosteroid treatment regimen used to treat children who have newly diagnosed ITP in most reported studies, and worldwide, is oral prednisone at a dose of 1 to 2 mg/kg per day given in divided doses and continued for a few weeks. Two randomized studies support the benefit of corticosteroid therapy in children who have ITP. In the first study, conducted by Sartorius [38] and reported in 1984, 73 children ages 10 months to 14 years who had newly diagnosed ITP were randomized to receive oral prednisolone ( $60 \text{ mg/m}^2$  per day for 21 days) or a placebo. Platelet responses were significantly faster in the corticosteroid-treated group, with 90% of children achieving a platelet count of  $30 \times 10^9/L$  within the first 10 days of treatment compared with 45% of children in the placebo no-treatment group. The Rumpel-Leede test, which measures capillary resistance (blood vessel integrity), became negative sooner in the corticosteroid-treated group. In the second study, reported by Buchanan and Holtkamp [39] in 1984, 27 children who had acute ITP were randomized to receive oral prednisone (2 mg/kg per day for 14 days, with tapering and discontinuation of corticosteroids by day 21) or placebo. Although there was a definite trend in favor of corticosteroids, only on day 7 of therapy did the prednisone-treated patients have significantly higher platelet counts, lower bleeding scores, and shorter bleeding times than children receiving placebo. Taken together, these two studies suggest limited early benefit from conventional dose oral corticosteroid therapy in children who have acute ITP.

The risks and benefits of high-dose corticosteroid therapy administered orally or IV to children who have acute ITP merit discussion. In a study of 20 children randomized to receive oral megadose methylprednisolone (30 mg/kg for 3 days followed by 20 mg/kg for 4 days) or IVIG (0.4 g/kg  $\times$  5 days), Özsoylu and colleagues [40] reported that 80% of children in both groups had platelet counts greater than  $50 \times 10^9/L$  by 72 hours after

the start of treatment. Corticosteroids were given before 9:00 AM and adverse effects were not observed. In contrast, Suarez and colleagues [41] reported that hyperactivity and behavioral problems occurred in 5 of 9 children who had acute ITP given 6 to 8 mg/kg per day of oral prednisone for 3 days or until platelet counts had increased to  $20 \times 10^9/L$ . Immediate platelet responses with this regimen were impressive: the mean time to achieve a platelet count of  $20 \times 10^9/L$  was  $1.9 \pm 0.6$  days (range 1–3 days).

A commonly used high-dose corticosteroid regimen is that reported by van Hoff and Ritchey [42]. The investigators treated 21 consecutive children who had ITP using IV methylprednisolone (30 mg/kg, maximum dose 1 g) given daily for 3 days. The median time to achieving a platelet count greater than  $20 \times 10^9/L$  was 24 hours. Ten children (48%) had transient glycosuria but no cases of hyperglycemia were observed. Similar results were reported by Jayabose and colleagues [43], who treated 20 children who had acute ITP with IV methylprednisolone (5 mg/kg per day in four divided doses). By 48 hours from start of treatment, 90% of children had platelet counts greater than  $20 \times 10^9/L$ , and all children achieved this hemostatic threshold by 72 hours from the start of treatment. No patients developed symptomatic hyperglycemia or hypertension; the investigators did not comment about weight gain or mood/behavioral changes. The authors' experience with short-course oral prednisone (4 mg/kg per day  $\times$  4 days without tapering) is complementary. Eighty-three percent of children who had acute ITP and platelet counts less than  $20 \times 10^9/L$  achieved a platelet count above  $20 \times 10^9/L$  within 48 hours of starting corticosteroid therapy (Fig. 6) [44].

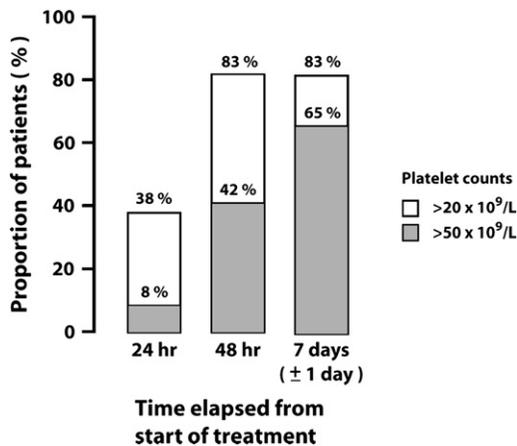


Fig. 6. Platelet response to short-course oral prednisone ( $4 \text{ mg kg}^{-1} \text{ d}^{-1}$  for 4 d) among 25 children who had acute ITP. (From Carcao MD, Zipursky A, Butchart S, et al. Short-course oral prednisone therapy in children presenting with acute immune thrombocytopenic purpura (ITP). *Acta Paediatr Suppl* 1998;424:71–4; with permission.)

On the basis of these studies, it can be concluded that a clinically significant increment in platelet count can be achieved rapidly in the majority of children who have acute ITP after the administration of high-doses of corticosteroids (approximately 4 mg/kg per day of prednisone or an equivalent corticosteroid preparation) administered orally or parenterally. The frequency and severity of corticosteroid toxicity relates to dose and duration of therapy and merits further study. If a decision is made to use corticosteroid therapy for children who have acute ITP, it seems wise to use high-dose corticosteroid regimens for as short a period of time as is necessary to achieve a clinically meaningful endpoint (eg, cessation of bleeding or achievement of a platelet count  $>20 \times 10^9/L$ ). This approach minimizes the predictable, and sometimes serious, adverse effects of long-term corticosteroid therapy (reviewed by Beck and colleagues [45]). A fall in platelet count often occurs during the period of tapering corticosteroids but not usually to clinically significant levels.

### *Intravenous immunoglobulin G*

Imbach and colleagues [46] first reported that IV infusion of a pooled, largely monomeric IgG preparation produced a rapid reversal of thrombocytopenia in children who had acute and chronic ITP. This landmark observation was confirmed subsequently by several investigators (reviewed by Blanchette and Carcao [22]). Transient blockade of Fc receptors on macrophages in the reticuloendothelial system, especially the spleen, is believed to play a major role in the immediate, and often dramatic, platelet responses observed after treatment of children who have ITP using a high dose of IVIG (1–2 g/kg). Two Canadian prospective randomized clinical trials are instructive in the context of IVIG treatment of children who have acute ITP. In the first study, reported by Blanchette and colleagues [47] in 1993, 53 children who had acute ITP and platelet counts less than  $20 \times 10^9/L$  were randomized to receive IVIG (1 g/kg on 2 consecutive days), oral prednisone (4 mg/kg per day  $\times$  7 days with tapering and discontinuation by day 21), or expectant management (no treatment). The rate of platelet response was significantly faster in children who received treatment compared with those managed expectantly; for the endpoint of time (days) taken to achieve a platelet count greater than or equal to  $20 \times 10^9/L$ , IVIG and corticosteroids were equivalent, whereas IVIG was superior to oral corticosteroid therapy for the endpoint of time (days) taken to achieve a platelet count greater than  $50 \times 10^9/L$ . Bleeding symptoms were not recorded in this study, however; the platelet count alone was used as a surrogate marker for response. The follow-up Canadian randomized trial compared two IVIG treatment regimens (1 g/kg on 2 consecutive days and 0.8 g/kg once), oral prednisone (4 mg/kg per day for 7 days with tapering and discontinuation by day 21), and for the subset of children who were blood group rhesus (D) positive, IV anti-D (25  $\mu$ g/kg on 2 consecutive days) [48]. The key

findings from this second randomized trial in children who had newly diagnosed ITP and platelet counts less than  $20 \times 10^9/L$  were (1) a single dose of IVIG (0.8 g/kg) was as effective as the larger dose of IVIG 1 g/kg for 2 days in raising the platelet count and (2) both IVIG regimens were superior to IV anti-D administered as 25  $\mu\text{g}/\text{kg}$  for 2 days for the clinically important endpoint of time (number of days) to achieve a platelet count greater than or equal to  $20 \times 10^9/L$ . Bleeding symptoms were not recorded in the study. The choice of the 0.8 g/kg dose as a single infusion reflected the early observation by Imbach and colleagues [49] that in children who had acute ITP treated with 0.4 g/kg of IVIG daily for 5 consecutive days, platelet responses often were observed after the first two infusions. These studies show that treatment with corticosteroids or IVIG can produce a rapid rise in the platelet count of children who have ITP with the caveat that the effect on bleeding symptoms was not assessed. As a result of these observations, the authors recommend that if a decision is made to treat children who have newly diagnosed ITP with IVIG, the initial dose should be 0.8 to 1.0 g/kg administered as a single infusion with subsequent IVIG doses given based on the clinical situation and follow-up platelet counts. Reflex administration of a second dose of IVIG (ie, a total dose of 2 g/kg) generally is not necessary and for the majority of children only leads to an increased frequency of adverse side effects (eg, headache, nausea, or vomiting) and higher costs.

It generally is accepted that IVIG therapy in children who have ITP, although expensive, is safe. High doses (2 g/kg), however, frequently are associated with side effects, principally fever and headache [47]. Other uncommon but clinically significant treatment-associated adverse effects include neutropenia and hemolytic anemia caused by alloantibodies in the IVIG preparations and self-limiting aseptic meningitis that generally occurs a few days after IVIG therapy. This latter complication is characterized by severe headache and, for the subset of children who still are significantly thrombocytopenic, often prompts investigation with a CT scan to rule out an ICH. On a reassuring note, although IVIG is a human plasma-derived product, current commercially available IVIG preparations are treated with highly effective measures to inactivate lipid-coated viruses, such as HIV and hepatitis C.

### *Intravenous anti-D*

In 1983, Salama and colleagues [50] reported that the IV infusion of anti-D resulted in the reversal of thrombocytopenia in patients who had ITP and were rhesus (D) positive. The investigators speculated that the beneficial effect of anti-D was due to the competitive inhibition of reticuloendothelial function by preferential sequestration of immunoglobulin-coated autologous red blood cells (RBCs). These observations subsequently were confirmed by several investigators. In a report that detailed experience with IV anti-D treatment in 272 subjects who had ITP, Scaradavou and colleagues [51] documented several important findings, including (1) anti-D at conventional

doses is ineffective in splenectomized subjects; (2) platelet responses are significantly better in children compared with adults; and (3) responders to IV anti-D generally respond on retreatment. There was a trend toward a higher platelet count after therapy in patients who received 40 to 60  $\mu\text{g}/\text{kg}$  of IV anti-D compared with those who received less than or equal to 40  $\mu\text{g}/\text{kg}$ . The dose response to IV anti-D is of importance. A recent report by Tarantino and colleagues [52], describing the results of a prospective randomized clinical trial of IV anti-D (50  $\mu\text{g}/\text{kg}$  and 75  $\mu\text{g}/\text{kg}$ ) and IVIG (0.8 g/kg) in 101 children who had acute ITP and platelet counts less than  $20 \times 10^9/\text{L}$ , clearly established that IV anti-D (75  $\mu\text{g}/\text{kg}$ ) is superior to IV anti-D (50  $\mu\text{g}/\text{kg}$ ) and equivalent to IVIG (0.8 g/kg) with respect to the numbers of cases with platelet counts greater than  $20 \times 10^9/\text{L}$  at 24 hours after therapy.

Short-term adverse effects, such as fever, chills, and nausea/vomiting, are more frequent with a 75- $\mu\text{g}/\text{kg}$  than a 50- $\mu\text{g}/\text{kg}$  dose and are likely related to release of pro-inflammatory cytokines/chemokines after IV anti-D [53]. These side effects can be ameliorated/prevented by premedication of patients with acetaminophen/corticosteroids. The most predictable adverse effect of anti-D therapy in subjects who are rhesus (D) positive is a fall in hemoglobin level due to RBC destruction by infused RBC alloantibodies. The fall in hemoglobin occurs within 1 week of the anti-D therapy with recovery generally evident by day 21. In the Scaradavou study, the mean hemoglobin decrease was 0.8 g/dL at 7 days post IV anti-D treatment, and only 16% of cases had a hemoglobin decrease greater than 2.1 g/dL [51]. In occasional cases, abrupt severe intravascular hemolysis is reported after therapy; the majority of these cases were in adults, some of whom had comorbid diseases [54]. This complication also is reported in rare cases after IVIG therapy. Physicians who treat children who have ITP using anti-D should be aware of this complication and advise parents and children to report symptoms and signs, such as excessive tiredness or pallor or passage of dark (tea-colored) urine, promptly. No clinically significant increase in treatment-related hemolysis has been reported with 75 versus 50  $\mu\text{g}/\text{kg}$  of IV anti-D, and a single dose of 75  $\mu\text{g}/\text{kg}$  of anti-D now can be recommended as standard dosing for the treatment of children who have acute ITP and are rhesus (D) positive.

### **To perform a bone marrow aspirate or not**

There is consensus that bone marrow aspiration is not necessary for children who have newly diagnosed typical acute ITP if management involves observation or plasma based therapies, such as IVIG or anti-D. The contentious issue is whether or not a bone marrow aspirate should be performed in children who have typical acute ITP before starting corticosteroids to avoid missing, and therefore treating inappropriately, an underlying leukemia. The results of a retrospective study of bone marrow aspirates performed in children who have suspected acute ITP are instructive in this regard [55]. No children who had typical laboratory features, defined

as a normal hemoglobin level and total white blood cell and neutrophil count for age, had underlying leukemia; cases of leukemia, however, were observed in children who had atypical laboratory features. A bone marrow examination, therefore, should be considered mandatory in atypical cases of childhood acute ITP, defined as those who have lassitude, protracted fever, bone or joint pain, and unexplained anemia, neutropenia, or macrocytosis. The diagnosis should be questioned, particularly in those children who fail to remit. The most common diagnosis to emerge after isolated thrombocytopenia in a well child is aplastic anemia.

### **To hospitalize or not**

The majority of children who have newly diagnosed acute ITP and platelet counts less than  $20 \times 10^9/L$  are hospitalized. The figure was 83% in the first United Kingdom National Survey [14] and 78% of 1995 children who had newly diagnosed ITP reported by Kühne and colleagues [12] on behalf of the ICIS. This high hospitalization rate is driven by the decision to treat and the perceived need for a bone marrow aspirate before starting corticosteroid therapy. If a conservative management approach is used, with bone marrow aspiration and treatment reserved for selected cases only (eg, those with atypical features or clinically significant bleeding), a low rate of hospitalization can be achieved [37]. Outpatient infusion of IVIG or anti-D also is an option in selected cases.

### **Chronic immune thrombocytopenic purpura**

Conventionally, chronic ITP is defined as thrombocytopenia (platelet count less than  $150 \times 10^9/L$ ) persisting for longer than 6 months from the onset of illness. Using this definition, approximately 20% to 25% of children manifest chronic ITP at 6 months after the initial diagnosis of ITP. Many children who have platelet counts in the range of 30 to  $150 \times 10^9/L$ , however, require no platelet-enhancing therapy and some enter a spontaneous complete remission in the 6 to 24 months after initial presentation [24]. The clinically important subgroup of children is those who have platelet counts less than or equal to  $20 \times 10^9/L$  at 6 months from initial diagnosis and who require ongoing platelet-enhancing therapy because of bleeding symptoms. This is the small group of children for whom second-line therapies (eg, rituximab) or splenectomy may need to be considered, approximately 5% of children who have acute ITP at the time point of 18 months after initial presentation [26].

### **Management**

#### *Presplenectomy management*

Medical management is preferred over splenectomy for children who have chronic ITP for less than 12 months. Treatment options include oral

corticosteroids (including pulse oral dexamethasone), IVIG, and IV anti-D (reviewed by Blanchette and Price [56]). Avoidance of medications known to affect platelet function adversely, especially aspirin, should be stressed and high-risk competitive or contact activities should be avoided during periods of severe thrombocytopenia. The goal should be to maintain a hemostatically “safe” platelet count while avoiding the potential toxicities and cost of overtreatment, in particular the well-known adverse effects of protracted corticosteroid therapy. If treatment is recommended, the authors’ preference is to use short courses of relatively high-dose oral prednisone (4 mg/kg per day for 4 days, maximum daily dose 180 mg), IVIG (0.8 to 1.0 g/kg once), or, for children who are rhesus (D) positive, IV anti-D (75 µg/kg once), with all treatments given intermittently based on clinical need. Treatment is, in the main, outpatient based and parents and children (if of an appropriate age) should be informed about the risk, benefits, and alternatives to treatment, including the remote risk for transfusion-transmitted infections with virus-inactivated plasma-based therapies, such as IVIG and IV anti-D. The advantage of anti-D over IVIG in this clinical setting relates to the ease of administration (anti-D can be infused over 5–10 minutes compared with several hours for IVIG), significantly lower cost in some countries, and a comparable platelet-enhancing effect.

### *Splenectomy*

Guidelines for splenectomy in children who have ITP are conservative, reflecting the significant spontaneous remissions that occur in children who have early chronic ITP and the small but finite risk of overwhelming postsplenectomy sepsis, a complication especially worrisome in children under 6 years of age. A group of United Kingdom pediatric hematologists recommended in 1992 that in children who have ITP, “splenectomy should not be considered before at least six months and preferably 12 months from the time of diagnosis, unless there are very major problems” [33]. New guidelines published in 2003 state that splenectomy rarely is indicated in children who have ITP but comment that “severe lifestyle restrictions, crippling menorrhagia and life-threatening hemorrhage may give good reason for the procedure” [36]. Practice guidelines developed for the American Society of Hematology (ASH) advocate that elective splenectomy be considered in children who have persistence of ITP for at least 12 months and who manifest bleeding symptoms and a platelet count below  $10 \times 10^9/L$  (children ages 3 to 12) or  $10$  to  $30 \times 10^9/L$  (children ages 8 to 12 years) [5]. Only a few scenarios were considered, however. The efficacy and relative safety of splenectomy led Mantadakis and Buchanan [57] to recommend splenectomy for children older than 5 years who have had symptomatic ITP longer than 6 months’ duration and whose quality of life is affected adversely by hemorrhagic manifestations, constant fear of bleeding, or complication of medical therapies. In contrast, the Israeli ITP Study Group recommends early

splenectomy in children not responding rapidly to corticosteroid therapy [58]. This seems premature as many children likely remit spontaneously given time.

If elective splenectomy is performed, the laparoscopic technique is preferred; accessory spleens often are present and should be removed at the time of surgical intervention. Preoperative treatment with corticosteroids, IVIG, or anti-D is considered appropriate for children who have platelet counts less than  $30 \times 10^9/L$ . The outcome after splenectomy in children who have primary ITP is good, and a complete remission rate of approximately 70% can be expected after the procedure (Table 2). Some of the children reported in these series, however, may have entered a spontaneous remission over time without splenectomy. In adults, potential predictors of success after splenectomy include imaging studies to document the sites of platelet destruction and the historical response to medical therapies, such as IVIG and IV anti-D [63–65]. The results of imaging studies are insufficiently specific, however, and reports of the predictive value of prior responses to medical therapies too conflicting to recommend that this information be used to determine reliably whether or not a splenectomy should be performed in children who have chronic ITP.

### Protection against overwhelming postsplenectomy infection

Before elective splenectomy, children who have ITP should be immunized with the hemophilus influenza type b and pneumococcal vaccines; depending on their age and immunization history, meningococcal vaccine also is recommended [66]. Because the protection provided after immunization is incomplete (not all pneumococcal serotypes are included in the currently available vaccines), daily prophylaxis with penicillin, or an equivalent antibiotic if the child is allergic to penicillin, is recommended for children up to 5 years of age and for at least 1 year after splenectomy to prevent pneumococcal sepsis, in particular. Some physicians recommend continuing antibiotic prophylaxis into adulthood. All febrile episodes should be assessed carefully and the use of parenteral antibiotics considered because overwhelming postsplenectomy

Table 2  
Complete remission rates after splenectomy in children who had immune thrombocytopenic purpura

	Number of cases	Complete remission (%)
ASH review [5]	271	72
Blanchette (1992) [59]	21	81
Ben Yehuda (1994) [58]	27	67
Mantadakis (2000) [57]	38	76
Aronis (2004) [60]	33	79
Kühne (2006) [61]	134	67
Wang (2006) [62]	65	89
	589	74

infection can occur despite immunization and use of antibiotic prophylaxis. Children should wear a medical alert bracelet indicating that they have had a splenectomy and when traveling abroad should carry an explanatory letter and a supply of antibiotics to be started in the event of a febrile episode while arranging for medical assessment. In the United Kingdom, patients are issued with a card stating that they are asplenic.

### Emergency treatment

On rare occasions, children who have acute ITP and severe thrombocytopenia may manifest symptoms or signs suggestive of organ- or life-threatening hemorrhage (eg, ICH). Management of such cases is challenging and should involve measures that have the potential to increase the circulating platelet count rapidly. An approach commonly used involves the immediate IV administration of methylprednisolone (30 mg/kg, maximum dose 1 g) over 20 to 30 minutes plus a larger than usual (two- to threefold) infusion of donor platelets in an attempt to boost the circulating platelet count temporarily. After administration of IV methylprednisolone and platelets, an infusion of IVIG (1 g/kg) should be started with IVIG and methylprednisolone repeated daily as indicated clinically, generally for at least 1 to 2 days. Survival of transfused donor platelets may be improved after IVIG therapy [67]. Depending on the specific clinical circumstances, an emergency splenectomy may need to be considered. Continuous infusion of platelets may be beneficial in selected cases. Experience with recombinant factor VIIa is limited but this hemostatic agent can be administered rapidly and should be considered in critical situations [68].

### Combined cytopenias

The combination of ITP and clinically significant autoimmune hemolytic anemia (Evans's syndrome) or autoimmune neutropenia occurs in a minority of cases [69–73]. Affected children often are older than those who present with typical acute ITP. The clinical course is variable and often prolonged

Table 3  
Retrospective reviews of patients who had Evans's syndrome

Investigator	Number of cases	Median age at onset (y)	Male:female ratio	Associated neutropenia	Number of deaths
Wang (1988) [69]	10	7.5	6:4	50%	3/10
Savaşan (1997) [70]	11	5.5	10:1	55%	4/11
Matthew (1997) [71]	42	7.7	22:20	38%	3/42
Blouin (2005) [72]	36	4.0	20:16	27%	3/36
	99		58:41	37%	13/99 (13.1%)

with significant morbidity and mortality reported in retrospective series (Table 3). Response to single-agent therapy or splenectomy often is poor [74]; combination immunosuppressive therapy may yield improved results [74–77]. Underlying causes for the combined cytopenias include SLE, CVID, and the autoimmune lymphoproliferative syndrome (ALPS). Malignancies (eg, Hodgkin's disease and lymphomas) and chronic infections (eg, HIV and hepatitis C) also need to be considered. The possibility of these conditions should be kept in mind in children who have combined immune cytopenias and appropriate investigations performed.

Features of CVID include recurrent bacterial infections (especially sinopulmonary), gastrointestinal disturbances similar to those seen in children who have inflammatory bowel disease, and granulomatous disease, especially affecting the lungs [78–82]. Laboratory features include low serum IgG levels and in some cases low serum IgA and IgM levels, absent or impaired specific antibody responses to infection or vaccination, and variable abnormalities of the immune system (eg, decreased numbers or function of T and B cells). Approximately 10% to 20% of subjects who have CVID manifest autoimmune cytopenias [79]. Treatment consists of regular IVIG replacement therapy [82]. Caution should be exercised about performing splenectomy in cases of CVID-associated ITP because of the risk for overwhelming postsplenectomy infection.

ALPS is a rare but important disorder because of defects in programmed cell death of lymphocytes [83–87]. Mutations in the Fas receptor, Fas ligand, and caspase genes are identified in approximately 70% of cases. Clinical features of the disorder include massive lymphadenopathy, most often in the cervical and axillary areas, and hepatosplenomegaly. The laboratory hallmark of ALPS is an increased number of double-negative (CD4-negative and CD8-negative) T cells that express the  $\alpha/\beta$  T-cell receptor. Defective *in vitro* antigen-induced apoptosis in cultured lymphocytes can be demonstrated in affected cases. For accurate diagnosis of ALPS, these tests should be performed by laboratories familiar with the test methods and in which local normal values are established [88]. The best frontline treatment of patients who have ALPS is with mycophenolate mofetil (MMF); in the largest series of ALPS reported to date of treatment with this immunosuppressive agent, a response rate of 92% was observed [89]. Splenectomy should be avoided in ALPS cases because of the high risk for overwhelming postsplenectomy sepsis.

### **New therapies**

First-line therapies in children include corticosteroids, high-dose IVIG, and, for children who are rhesus positive, IV anti-D. Splenectomy is the traditional second-line treatment of those children who have well-established, symptomatic chronic ITP who have failed or are intolerant of first-line therapies. An array of third-line therapies is available for children in whom

splenectomy is refused or contraindicated. Agents include azathioprine, cyclophosphamide, danazol, vinca alkaloids, dapsone, cyclosporine, MMF, or combination therapy. As with adults, current evidence supporting effectiveness and safety of these therapies in children who have severe chronic refractory ITP is minimal [5,90]. The decision to choose one of these agents or combinations usually is based on physician preferences and experience. A major difficulty with many of these third-line therapies is modest response rates and frequently a slow onset of action. In addition, bone marrow suppression and an increased incidence of infection complicate treatment with many of the immunosuppressive agents. Before physicians can confidently know the best management for their patients, these treatments, and perhaps combinations of agents and new approaches to treatment, must be evaluated for effectiveness and safety in prospective cohort studies of consecutive patients or randomized controlled trials. Such trials should include measurement of relevant clinical outcomes (eg, bleeding manifestations and quality of life) other than the platelet count alone [90].

Rituximab is a human murine (chimeric) monoclonal antibody directed against the CD20 antigen expressed on pre-B and mature B lymphocytes. Rituximab eliminates most circulating B cells with recovery of B-cell counts 6 to 12 months after therapy. Rituximab currently is indicated for the treatment of lymphoma in adults. Because of its ability to deplete autoantibody-producing lymphocytes, it is used off-label to treat patients who have a variety of autoimmune diseases. Experience with rituximab therapy for patients who have ITP is greatest for adults. In a recent systematic review that involved 313 patients from 19 studies, Arnold and colleagues [91] reported a complete response rate, defined as a platelet count greater than  $150 \times 10^9/L$ , in 43.6% of cases (95% CI, 29.5% to 57.7%); 62.5% of cases (95% CI, 52.6% to 72.5%) achieved platelet counts greater than  $50 \times 10^9/L$ . The treatment regimen used most frequently was  $375 \text{ mg}/\text{m}^2$  administered weekly for 4 weeks. The median time to response was 5.5 weeks and the median response duration 10.5 months. Durable responses were more frequent in patients who achieved complete remission. The largest pediatric series reported data including 36 patients, ages 2.6 to 18.3 years, six of whom had Evans's syndrome [92]. Responses, defined as a platelet count greater than  $50 \times 10^9/L$  during 4 consecutive weeks starting in weeks 9 to 12 after 4 weekly doses of rituximab ( $375 \text{ mg}/\text{m}^2$  per dose), were observed in 31% of cases (CI, 16% to 48%). In adults who had chronic ITP, durable responses lasting longer than 1 year were more likely in complete responders, and these patients also were more likely to respond to retreatment after relapse [93,94]. Although these results are promising, there is an urgent need for randomized control trials to define the role of rituximab as a splenectomy-sparing strategy or as treatment of patients who fail splenectomy and who have severe, symptomatic ITP. Clinically severe, short- and medium-term adverse effects after rituximab therapy for patients who have ITP fortunately are rare. They include therapy-associated serum sickness, immediate and delayed neutropenia, and

reactivation of coexisting chronic infections (eg, hepatitis B) [95,96]. The recent report of two patients who had SLE who developed progressive multifocal leukoencephalopathy after rituximab therapy prompted an alert from the Food and Drug Administration's MedWatch Program [96]. Although changes in circulating immunoglobulin levels are observed in some children after rituximab therapy, it seems that IVIG replacement therapy for otherwise healthy pediatric patients who have ITP and who do not have underlying immunodeficiency treated with rituximab is unnecessary [92].

TPO is the primary growth factor in regulation of platelet production [97]. Megakaryopoiesis is controlled by signaling through the c-Mpl receptor present on megakaryocytes and platelets. On the basis that platelet production is impaired in some patients who have ITP, studies evaluated the use of a pegylated, truncated form of human TPO (PEG-megakaryocyte growth and development factor [MGDF]) with encouraging results. PEG-MGDF was immunogenic and induced production of neutralizing anti-TPO antibodies in some recipients, resulting in thrombocytopenia [98]. It was withdrawn, therefore, from further clinical investigation. Recently, nonimmunogenic thrombopoietic peptides (AMG 531) and small nonpeptide molecules (eltrombopag and AKR-501) have been developed [99] (reviewed by Kuter [100]). AMG 531 consists of a peptide-binding domain, which stimulates megakaryopoiesis in the same way as TPO, and a carrier Fc domain. AMG 531 activates c-Mpl receptors to stimulate the growth and maturation of megakaryocytes and this effect ultimately results in increased production of platelets. Preliminary studies with AMG 531 in adults who have ITP are encouraging [101,102]. A prospective pediatric study is underway. Eltrombopag and AKR-501 are small-molecule thrombopoietic receptor agonists administered orally [99]. Early results with eltrombopag in adults who have ITP also are encouraging [103]. Apart from reversible marrow fibrosis in some adult patients treated with AMG 531, these novel platelet-enhancing therapies seem remarkably nontoxic. Their true place in the management of children who have ITP remains to be determined through prospective clinical trials. It should be borne in mind that, based on experience in adults, recurrence of thrombocytopenia in cases of chronic, refractory ITP is likely in most cases once these novel thrombopoiesis-stimulating agents are discontinued.

### **Future directions**

Although much has been learned about the pathogenesis and treatment of ITP over the past 3 decades, many questions remain unanswered. Optimal management of children who have newly diagnosed acute ITP and platelet counts less than  $20 \times 10^9/L$  remains the subject of debate and there is an urgent need for a well-designed large trial to address the issues of to treat or not, to perform a bone marrow aspirate or not, and whether or not to hospitalize such children. Experience from the United Kingdom suggests

that promotion of conservative guidelines for management of childhood acute ITP can result in a decrease in the frequency of treatment and invasive procedures, such as bone marrow aspirates [104]. The role of new therapies, such as rituximab and thrombopoietic agents, remains to be defined by well-designed, prospective clinical trials. All future clinical trials for childhood ITP should include outcome measures more than the platelet count alone (eg, bleeding scores, health-related quality-of-life assessments, and economic analyses) [105–111]. Finally, exchange of information between adult and pediatric hematologists who care for patients who have ITP must be encouraged, especially with regard to guidelines for investigation and management [112].

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