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REVIEW ARTICLE

Acute immune thrombocytopenic purpura in children

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ABSTRACT

Immune thrombocytopenic purpura (ITP) in children is usually a benign and self-limiting disorder. It may follow a viral infection or immunization and is caused by an inappropriate response of the immune system. The diagnosis relies on the exclusion of other causes of thrombocytopenia. This paper discusses the differential diagnoses and investigations, especially the importance of bone marrow aspiration. The course of the disease and incidence of intracranial hemorrhage are also discussed. There is substantial discrepancy between published guidelines and between clinicians who like to over-treat. The treatment of the disease ranges from observation to drugs like intravenous immunoglobulin, steroids and anti-D to splenectomy. The different modes of treatment are evaluated. The best treatment seems to be observation except in severe cases.

Key Words: Thrombocytopenic purpura, bone marrow aspiration, Intravenous immunoglobulin therapy, steroids, anti-D immunoglobulins

INTRODUCTION

Immune thrombocytopenic purpura (ITP) in children is usually a self-limiting disorder. The American Society of Hematology (ASH) in 1996 defined ITP as isolated thrombocytopenia with no clinically apparent associated conditions and no other cause of thrombocytopenia, e.g., human immunodeficiency virus (HIV) infection, systemic lupus erythematosus, lymphoproliferative disorders, myelodysplasia, agammaglobulinemia, hypogammaglobulinemia, drug-induced thrombocytopenia, alloimmune thrombocytopenia, and congenital/hereditary nonimmune thrombocytopenia [1]. The other terms used for ITP are immune-mediated thrombocytopenic purpura and idiopathic thrombocytopenic purpura.

The classical clinical features include a previously well child with sudden onset of excessive bruising, petechiae and or mucous membrane bleeding 1-4 weeks following a viral infection or an immunization. Kuhne *et al.* 2003 [2] reported an infection in 60.2% of cases preceding the disease in children one to 10 years of age. Both genders are equally affected. Fever, lethargy, weight loss, bone pains, joint pains, pallor, lymphadenopathy and hepatosplenomegaly are characteristically absent. Minimal splenomegaly occurs in about 5 to 12% of symptomatic children [3,4] but marked splenomegaly is typically absent.

Chronic ITP is the term given to the disease if it persists more than six months [5,6] while recurrent ITP is defined as the recurrence of ITP after a prolonged period (at least 3 months) of clinical remission sustained without any treatment [7]. Such recurrences is seen in approximately 4% of children with ITP. It can occur after acute or chronic course of ITP [8]. The incidence of the is about 3-10 per 100,000 children per year below 16 years of age [9]. Both genders are equally affected. Data from Maryland [10] showed prevalence of ITP in 1-4 years age group as 9.3 per 100 000 people, 6-11 years age group as 7.3 and 11-14 years as 4.1 per 100 000 people. There was a predominance of males in childhood.

PATHOGENESIS

Immune thrombocytopenic purpura is caused by an inappropriate response of the immune system usually following a viral infection or immunization. Although ITP is primarily mediated by IgG autoantibodies, the production of these autoantibodies is regulated by the influence of T lymphocytes and antigen-presenting cells (APC). There is evidence that enhanced T-helper cell/APC interactions in patients with ITP may play an integral role in IgG antiplatelet autoantibody production [11]. Some patients have evidence of oligoclonality whereas others have polyclonal autoantibodies [12]. ITP patients develop autoantibodies that bind to platelet antigens (such a glycoprotein IIb/IIIa (GPIIb/IIa) or GPIb/IX) and mediate platelet destruction via the reticuloe dothelial system (RES) [13]. Immune-mediated clearance of particles is a function of immunoglobulin class, complement activation, and specific effector cells within the RES [14]. Three discrete pathways may result in the destruction of antibodycoated platelets. In one path-way, the direct activation of the complement cascade results in the formation of a membrane attack complex that produces pores in the platelet membrane and subsequent platelet lysis. Platelet destruction may also occur via engagement of complement receptors (CR1), Fcγ receptors (FcγR), or both [15]. The role of FcγR for eliminating platelets in ITP patients has been well documented [16]. Fcγ chain deficient mice cannot develop ITP [17], and ITP is palliated by therapy with anti-FcγR antibodies [18] and Fcγ fragments of intravenous immunoglobulin [19]. However, the role of complement in pathogenesis of ITP is not yet clear [20]. Several studies have shown that ITP patients demonstrate elevated levels of platelet-associated C3, C4, and C9, suggesting in vivo complement activation [21], and some of the effects of IVIG may occur by reducing C3 and C4 deposition on platelets [22]. Additionally, it has been suggested that FcγR-mediated platelet elimination most likely occurs in the spleen and that complement-mediated platelet elimination most likely occurs in the liver; as such, complement-mediated platelet elimination may be of particular importance in splenectomized ITP patients. The competitive blockade of Fcγ R reduces Fcγ R-mediated elimination of platelets, thereby increasing platelet counts in ITP [23] is the basis of present (anti-D) and possible future treatments like antibody-coated liposomes [24].

GENETICS AND ITP

There is emerging evidence that genetics can play a major role in the development and clinical outcome of this disease Rischewski JR *et al* [25] noted a high number of ITP patients with a positive family history indicating the likely existence of a genetic susceptibility for ITP. Sood R *et al* 2006 [26] studied the whole blood gene expression profile in five ITP patients and five control samples. Using DNA micro arrays that

contained 24,473 unique putative genes, it was found that176 cDNAs were strongly correlated with ITP. These included a cluster of interferon-regulated genes and TLR7, as well many less-well characterized genes which are candidates for further study.

Carcao MD *et al* [27] noted that the Fcgamma RIIa-131H and the FcgammaRIIIa-158V were significantly over-represented in children with ITP versus the control subjects. The same statistical difference was noted with the combined FcgammaRIIa-131H and FcgammaRIIIa-158V allelic gene frequencies. Wu KH *et al* 2005 [28] suggested that the IL-4 intron 3 and IL-10 (-627) polymorphisms contribute to the susceptibility of developing childhood chronic ITP.

CLINICAL CLASSIFICATION

Immune thrombocytopenic purpura may be classified [6] according to the severity of the disease:

Type A or asymptomatic-pauci-symptomatic: symptoms ranging from no bleeding to few petechiae and some bruises without mucosal hemorrhages. Type B or intermediate: clinical picture with more petechiae, bruising and mucosal hemorrhages.

Type C or severe: clinical picture with severe cutaneous and mucosal bleeding symptoms with at least one of the following features: retinal hemorrhages, intracranial hemorrhage (ICH), other severe internal hemorrhages, hemorrhagic shock, and life-threatening bleeding.

INVESTIGATIONS and DIAGNOSIS

The diagnosis depends upon the exclusion of other causes of thrombocytopenia. A pseudothrombocytopenia due to in vitro platelet agglutination in the presence of EDTA ought to be ruled out from the true thrombocytopenia.

Complete blood count and peripheral smear

A complete blood count (CBC) and examination of the peripheral blood smear are essential for the diagnosis. The CBC demonstrates isolated (and often profound) thrombocytopenia. Some children may be anemic due to blood loss. Approximately 10% of children have transient absolute neutropenia [29]. Platelets may be normal or larger in size but consistently giant platelets (approaching the size of red blood cells) are absent There should be normal red blood cell morphology and normal white blood count and morphology. The features which are not consistent with the diagnosis of ITP include predominant giant platelets, polychromatophilia (unless response to bleeding), macrocytes, and nucleated red blood cells. There may be eosinophilia [6]. Some children may have an increased number of normal or atypical lymphocytes on the peripheral smear reflecting a recent viral illness.

Bone marrow aspirate

There is general consensus that bone marrow aspiration is not indicated in a typical case [1], but it should be done if there is any doubt about the diagnosis [30,31], if steroids are to be given for the treatment [32,33], or in infants with Down's syndrome in whom thrombocytopenia may herald the development of megakaryoblastic leukemia [34]. The purpose of bone marrow investigation is to exclude the other causes of thrombocytopenia. Watts 2004 studied the bone marrow in 72% of cases but the diagnosis remained the same [35]. The bone marrow examination, when done, reveals normal granulocytic and erythrocytic series with characteristically normal or increased number of megakaryocytes.

Kuwana M *et al* [40] developed laboratory based diagnostic criteria which had 98% sensitivity, 79% specificity, a 95% positive predictive value, and a 90% negative predictive value. It includes two criteria, both of which should be fulfilled:

Thrombocytopenia (<100000 per μl) without morphologic evidence for dysplasia in the peripheral blood film and the presence of any three or more, including at least one of (iii), (vi), and (iv), of the following laboratory findings:

(i) absence of anemia, (ii) normal leukocyte count, (iii) increased anti-GPIIb/IIIa antibody producing B cell frequency, (vi) increased platelet-associated anti-GPIIb/IIIa antibody level, (v) elevated percentage of reticulated platelets, and (iv) normal or slightly increased plasma Thrombopoitin level (<300 pg per ml).

Other investigations

The antiplatelet antibodies assays have no value in the diagnosis or prognosis of the disease [17,36,37,38]. Flow cytometry is also non-specific for establishing the diagnosis [39]. Other investigations like antinuclear antibody, direct antiglobulin antibody test, HIV, mean platelet volume, and

reticulocyte counts are also not included in the routine workup of establishing the diagnosis [1].

DIFFERENTIAL DIAGNOSIS

A clear history of acute onset of purpura and/or bruising in an otherwise well child, together with careful examination and the blood film is essential to exclude other diagnoses. Acute leukemia, aplastic anemia and myelodysplastic syndromes rarely present with a low platelet count alone. Congenital thrombocytopenias (CTP) may be missed if not considered in the differential diagnosis. The following are the reasons to suspect CTP [41]:

a) Family history of thrombocytopenia.
b) Lack of platelet response to ITP therapies including intravenous immunoglobulins (IVIG), IV anti-D and steroids. There is no well-defined response threshold. Arbitrarily, a peak platelet >30,000/µl increase from baseline will rule out CTP while <10,000/µl peak increase is compatible with CTP or with a diagnosis of "refractory" ITP. Numbers in between are more ambiguous.
c) Diagnostic features on smear such as abnormal size of platelets (small, large, or giant), absence of platelet alpha granules (gray platelets) or Döhle-like bodies or microcytosis.
d) Bleeding out of proportion to the platelet count.
e) Onset at birth.
f) Associated clinical features such as absent radii, mental retardation, and renal failure, high tone hearing loss, cataracts, or the development of leukemia.
g) Persistence of a stable level of thrombocytopenia for years.

Older children, particularly those having a chronic course, should be investigated for signsand symptoms of systemic lupus or antiphospholipid syndrome. Children with hemorrhagic varicella and thrombocytopenia should be reviewed cautiously because of the rare but life-threatening association with acquired protein S deficiency and microvascular thrombosis [22]. History of drug administration, e.g. heparin, quinidine or quinine, cephalosporins, and rifampicin, etc., should also be elicited to rule out drug- induced thrombocytopenia.

Children with lymphoproliferative disorders may present as thrombocytopenia but they are usually sick looking with recurrent upper and lower respiratory tract infections, possibly gastro esophageal reflux, and failure to thrive. Family history is often positive for ITP or for other autoimmune diseases such as thyroiditis, diabetes or systemic lupus erythematosus. In this type of patient there is commonly a coexistent immune deficiency or dysregulation [43].

Disseminated Intravascular Coagulation frequently accompanies a severe systemic disease process and is characterized by thrombocytopenia, prolonged prothrombin, partial thromboplastin and thrombin time due to consumption coagulopathy. There may be associated microangiopathic hemolytic anemia.

VonWillibrond Disease type2b is also characterized by abnormal bleeding tendency due to rapid clearance of plateletlets and vonWillibrond factor so the diagnosis is based on demonstrating thrombocytopenia with low von Willibrond factor.

Thrombotic thrombocytopenic is very rare in children and is pentad of fever, microangiopathic hemolytic anemia, thrombocytopenia, abnormal renal function and central nervous system changes.

Hemolytic-Uremic Syndrome is characterized by microangiopathic hemolyticanemia, thrombocytopenia and renal failure. It is usually following an acute episode of gastroenteritis, often triggered by Escherichia coli 0157:H7.

INTRACRANIAL HEMORRHAGE AND ITP

Intracranial hemorrhage (ICH) is extremely rare. The majority of ICH events do not occur during the first few days after diagnosis but later in the course of the disease [9,44,45]. Butros *et al.* 2003 [45] reviewed 75 published cases of ICH with ITP from 1954 to 1998. Sixty-two cases ranged from 6 months to 20 years of age. ICH in 72% of cases occurred within six months of diagnosis, but only 7 (10%) occurred within three days of diagnosis. The platelet count was less than 10000/ul in 71.4% of the cases. In some studies on ITP [46,47], no case with life-threatening hemorrhage was found. No case of ICH and death due to ITP occurred in Germany from Oct 1995 to Sep 1997 [48]. Iyori *et al.* 2000 [49] did not find any correlation with either the severity of bleeding symptoms or the platelet count at the onset

of ICH. It occurred in children even on treatment [2,45,50-52] and was not always fatal [2,53]. But Arya *et al.* 2002 [33] reported high mortality due to ICH despite use of IVIG or high-dose corticosteroids in his patients. It had been shown that severely affected cases were not as responsive to treatment as the typical cases with acute ITP in whom platelet counts often increased overnight with therapy [55].

DISEASE COURSE

In 75-90% of cases, complete remission occurs irrespective of the treatment given [46,56,57]. Thrombocytopenia persisted for more than six months in only 10-25% of cases, showing a chronic course which also had a high rate of remission over time, up to 80% or even more [56]. Low admission mean platelet volume (<8 fL), a history of a viral prodrome [57,58] and low admission platelet count (<10,000/ul) correlated with high rate of remission [35,57,58], while the insidious onset of bruising [59] and diagnosis at 10-18 years [2,35,59] were more likely to be associated with a chronic clinical course. Gadner 2001 [56] demonstrated that initial therapy did not prevent the chronic course of the disease. The reported mortality in ITP is 0.1-0.5% [60].

MANAGEMENT

The emphasis is focused on efforts to treat or forestall bleeding without excess drug-induced toxicity or burden to the patient. The problem with all these treatments is that they do not treat the underlying disorder, only the low count, so relapse is common [5] and they do not change the prognosis [61,62]. There is substantial discrepancy among published guidelines [1,63] and among clinicians who like to over- treat the disease [32,33].

Explanation of the clinical course of ITP to the parents of the affected child is necessary. It is important to temporarily restrict motor activities, to avoid contact sports, to avoid some procedures (e.g. dental extractions) and not to use certain drugs like aspirin and ibuprofen which may worsen bleeding symptoms. It is advised to present to the hospital in the event of accidents.

The best treatment is OBSERVATION, except in clinical type C. Some like to treat clinical type B or clinical type A with platelet count <20000/ul with drugs because of the unproven fear of ICH at this low platelet count [5]. If the clinical type is A or the platelet count is >20000 /ul, observation is best. Children with platelet count less than 20000/ul or clinical type B or C need to be hospitalized [6].

Intravenous immunoglobulin (IVIG)

IVIG is a product manufactured from pooled human plasma and typically contains more than 95% unmodified immunoglobulin G (IgG), which has intact Fc-dependent effector functions and only trace amounts of immunoglobulin A (IgA) or immunoglobulin M [64]. IVIG increases the platelet count more rapidly than both no specific treatment and oral glucocorticoid therapy [65]. Meta-analysis done by Beck *et al.* 2005 [66] showed that children treated with corticosteroids were 26% less likely to have a platelet count >20,000/ul after 48 hours of therapy when compared with children treated with IVIG. Ancona *et al.* 2002 [61] in his randomized study showed that IVIG (1 g/kg/dose x 1-2 days) was effective in 80% of cases while methylprednisolone (MP) (30 mg/kg/dose for 2-3 days) was effective in 60% of cases in increasing platelet count above 50,000/ul within 48 hours, but without any difference at one week or later; no serious bleeding was noted in either of the treatment groups.

The exact mechanism of action of IVIG is not known. IgG may be involved in occupying the Fc receptors on reticuloendothelial cells, resulting in survival of the opsonized platelets. Another mechanism of action may be the presence of anti-idiotypic antibodies in the pooled IgG preparations, which bind to circulating autoantibodies, rendering them ineffective for platelet opsonins, and may also suppress the B-cells that produce the offending autoantibodies [4]. Teeling *et al.* in 2001 [67] demonstrated in animals that IgG dimers present in IVIG preparations were responsible for the increase in platelet counts. The effect of IVIG on the platelet count lasts between two to six weeks. The recommended regimen is 0.8 g/kg for one day. In very severe cases, a total dose of 2 g/kg divided in 2-5 days can be used [68,69]. The 0.8 g/kg posology achieves the same results as the dose of 400 mg/kg for five consecutive days but costs less, is more convenient and may have fewer side effects [68,70]. Another regimen may be 0.25 to 0.5 g/kg for two days and this was associated with fewer side effects [71], but the randomized study done by Benesch *et al.* 2003 [72] reported that platelet counts increased more rapidly after IVIG (1 g/kg/day x 2 days) as compared with 0.3 g/kg/day x 2 days dose.

Adverse effects of IVIG are common (15% to 75%) but generally mild. Most of the adverse reactions are primarily related to infusion rate, activation of complement and anaphylactic reactions to a component of the product [73]. These include flu-like reactions like low-grade fever, chills, muscle aches, fatigue and backache. Rare complications include aseptic meningitis, alloimmune hemolysis, hepatitis C infection, renal failure and anaphylaxis. However, no hepatitis C infection has been reported with viral inactivated products [1,4,74]. Niebanck *et al.* 2005 [75] in his randomized study noted that neutropenia (ANC <1500/ul) developed in 18% of cases treated with IVIG, which was likely to be a transient condition. Kattamis *et al.* 1997 [76] reported that 34% of cases treated with IVIG had transient neurological complications, manifested by severe headache, nausea, and, rarely, aseptic meningitis. Retrospective analysis of data by Jayabose *et al.* 1999 [77] showed that a short course of prednisone (2 mg/kg/day during and for 3 days after the completion of IVIG therapy) decreased the incidence and severity of neurological complications of IVIG.

There have been 26 reported cases of suspected hemolytic reactions associated with immune globulin [78]. The US Food and Drug Administration from June 1985 to November 1998 received 120 reports worldwide of acute renal failure which might be irreversible and occurred with the sucrose-stabilized formulation, but not with the D-sorbitol–stabilized formulation [79].

IVIG may be contra-indicated in patients with IgA deficiency as it may cause anaphylaxis due to presence of trace amounts of IgA. The live virus vaccines (except yellow fever vaccine) should only be given at least three weeks before or three months after an injection of IVIG [80].

Steroids

When compared with placebo, corticosteroid administration was associated with an earlier rise in platelet count as compared to when no therapy was administered [1,81]. For patients with acute ITP, a short course of high-dose corticosteroids, using either an oral or intravenous preparation, results in a clinically significant increment in platelet count without excessive steroid side effects [82]. The mechanism of action of glucocorticosteroids is thought to be multifactorial: they can increase vascular stability and platelet survival, an effect attributed to both decreased production of antiplatelet antibodies and decreased clearance of opsonized platelets [36].

The dose regimens include oral glucocorticoids 2 mg/kg/d or 60 mg/m^2/d of prednisone for 14 days, followed by a tapering down dose and discontinuation on day 21 [81] or 4 mg/kg/d in three divided doses for seven days, followed by a 50% reduction in the dose in the second week, and then by a tapering down dose and discontinuation on day 21 [68].

Other regimens include intravenous glucocorticoids as 15-30 mg/kg of MP administered over 30-60 minute bolus injection for three days with max dose of 1 g/d [83,84]. Platelet count recovery achieved by using high-dose parenteral glucocorticoids was faster than that obtained by oral glucocorticoids and was as rapid as that with IVIG [83-85]. Albayrak *et al.* 1994 [86] in his randomized study showed that IVIG (0.5 g/kg per day for 5 consecutive days), mega-dose MP (orally administered MP 30 mg/kg per day for 7 days or orally administered MP 50 mg/kg per day for 7 days) were equally effective.

Duru *et al.* 2002 [62] studied IVIG, mega-dose MP, or no therapy and showed that platelet counts at three days after starting therapy were significantly higher in both IVIG and mega-dose MP groups than in the no therapy group ($p<.01$), but there was no difference between the three groups at 10 and 30 days after initiation of therapy.

Although short courses utilized in childhood ITP are not commonly associated with the side effects of weight gain, sleep disturbance, hypertension and hyperglycemia, careful monitoring is still needed [82]. Sixty-two percent of patients receiving steroids reported side effects, compared with 31% receiving IVIG and 11.6% receiving anti-D. Most of the side effects in those receiving steroids were mild and included gastritis, weight gain, sleep disturbances, moodiness, and fatigue [87].

Anti-D immunoglobulin

Although the effect of anti-D on platelet count is generally not as long-lived as that of IVIG, many practitioners prefer its ease of administration (IV push). A retrospective analysis by Micheal *et al.* [70] showed that 50 μg/kg of anti-D compared favorably with IVIG (1 g/kg). Tarantino *et al.* 2006 [88] in a randomized study found that single 75 ug/kg dose of anti-D was better in raising the platelet count than standard-dose anti-D (50

ug/kg dose) and was as effective as IVIG (0.8 g/kg) with an acceptable safety profile. The mechanism of action is said to be that RBC-antibody complexes bind to macrophage Fc receptors and interfere with platelet destruction, thereby causing a rise in platelet count within two days.

Adverse events include headache, nausea, chills and fever. Sixteen percent of adult and pediatric patients developed hemolysis [89,90] with a mean hemoglobin drop of 0.8 g/dl seven days after treatment with anti-D. Christopher *et al.* 2005 [91] reported a case of irreversible encephalopathy 48 hours following an infusion of IV anti-D for ITP. It can only be used in Rh-(D) positive patients who have not undergone splenectomy. If the patients on anti-D therapy are to be transfused, only Rh-D negative red blood cells should be used to avoid exacerbation of ongoing hemolysis. It must be used with extreme caution in patients with a hemoglobin level less than 8 g/dl. While the effects on an Rh(D)-positive fetus are unknown, avoiding the use of intravenous RhIG in this situation until safety data are available is advisable [92].

Anti-CD20 (rituximab)

There is an emerging experience with anti-CD20 (rituximab) in the treatment of acute and chronic ITP. An early, encouraging case report was of an infant with severe, life-threatening ITP who had a sustained response after receiving anti-CD20 [93]. More recently, 375 mg/m^2 of rituximab in four weekly doses in 24 patients aged 2-19 years with chronic ITP was reported to induce a complete response in more than half of the patients, and the response lasted 4-30 months [94].

Splenectomy

Splenectomy is recommended in acute ITP for very rare cases with life- threatening hemorrhage when other therapies fail to give any benefit. Guidelines from the ASH and practice guidelines in the United Kingdom [95] recommend that splenectomy be considered for children who have had ITP for at least one year with symptomatic severe thrombocytopenia.

The acute risks include portal vein thrombosis, bleeding, and the longer-term risk for overwhelming sepsis. The clinician must carefully assess the patient's potential for eventual recovery without surgery especially in chronic, mild-moderate pediatric ITP. The failure rate after splenectomy is about 25-30%, and is probably more (up to 60%) with longer follow-up [6].

Recombinant factor VII

There is promising role of recombinant factor VII in the management of refractory severe hemorrhage both in acute as well as chronic ITP [96, 97].

Platelet transfusion

Platelet transfusion has little benefit in ITP, since platelet autoantigens are public antigens and present on all normal platelets. After a transfusion, there is usually no significant rise in platelet count, although exceptions can occur.

Severe and life-threatening bleeding

Neurological symptoms, internal bleeding, or emergency surgery demands immediate intervention. MP (30 mg/kg/d for two to three days intravenously) together with IVIG (1 g/kg/d for two to three days) and an infusion of platelets that is two to three times the usual amount infused may be used; vincristine may be considered as part of combination therapy [1,98]. Dexamethasone 1-2 mg/kg may be used in place of MP [1]. The role of emergency splenectomy is controversial [1,98]. Plasmapheresis is of limited benefit. For severe persistent bleeding, the course of high-dose IVIG can be extended to five days, along with continuous infusion of platelets (1 unit per hour) [98].

Management of first relapse

Given the lack of evidence that medical therapy favorably alters the long-term outcome, the goal is to maintain a safe platelet count [3]. All the above-mentioned treatments can be considered for every single episode of ITP within six months from the onset of the disease. At the end of each treatment (the day after the last administration of the drug or the 11th day in the case of no drug), the patient's clinical picture and platelet count should be reassessed. If the need to treat persists or a new episode occurs within six months from the onset of the original disease, it is recommended that treatment options are alternated [6]. In Rh-positive children, anti-D IG is preferred to IVIG because of its ease of administration, similar efficacy, and lower cost. Response rates of approximately 70% are seen and often last at least three weeks [89]. Long-term

corticosteroid therapy causes unacceptable adverse effects, and the frequency of durable responses to pulses of oral dexamethasone is disappointing. Splenectomy is deferred as long as possible [95] because one-third of children have spontaneous remission [1] and only 5% still have severe thrombocytopenia requiring therapy one year after diagnosis [99].

In brief, to date, virtually all of the randomized clinical trials conducted in children with ITP have focused on platelet counts as the sole outcome measure. Only carefully designed, multicenter, randomized clinical trials comparing the effects of different treatment modalities in terms of bleeding, quality of life, adverse effects, and treatment-related costs will be able to address the controversies surrounding childhood ITP treatment and allow management of this condition to be based on scientific data rather than treatment philosophy.

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