

blood

2010 115: 168-186
Prepublished online Oct 21, 2009;
doi:10.1182/blood-2009-06-225565

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International consensus report on the investigation and management of primary immune thrombocytopenia

Drew Provan,¹ Roberto Stasi,² Adrian C. Newland,¹ Victor S. Blanchette,³ Paula Bolton-Maggs,⁴ James B. Bussel,⁵ Beng H. Chong,⁶ Douglas B. Cines,⁷ Terry B. Gernsheimer,⁸ Bertrand Godeau,⁹ John Grainger,¹⁰ Ian Greer,¹¹ Beverley J. Hunt,¹² Paul A. Imbach,¹³ Gordon Lyons,¹⁴ Robert McMillan,¹⁵ Francesco Rodeghiero,¹⁶ Miguel A. Sanz,¹⁷ Michael Tarantino,¹⁸ Shirley Watson,¹⁹ Joan Young,²⁰ and David J. Kuter²¹

¹Department of Haematology, Barts and The London School of Medicine and Dentistry, London, United Kingdom; ²Department of Haematology, St George's Healthcare, National Health Service (NHS) Trust, London, United Kingdom; ³Division of Haematology/Oncology, University of Toronto, The Hospital for Sick Children, Toronto, ON; ⁴Department of Clinical Haematology, Manchester Royal Infirmary, Manchester, United Kingdom; ⁵Department of Pediatrics, New York Hospital, New York, NY; ⁶St George Clinical School, University of New South Wales, Sydney, Australia; ⁷Department of Pathology and Laboratory, Hospital of the University of Pennsylvania, Philadelphia; ⁸Puget Sound Blood Center and The University of Washington, Seattle; ⁹Service de Médecine Interne, Assistance-Publique Hôpitaux de Paris, Paris, France; ¹⁰Royal Manchester Children's Hospital, Manchester, United Kingdom; ¹¹Hull York Medical School, University of York, York, United Kingdom; ¹²Thrombosis & Haemostasis, King's College, London, and Departments of Haematology, Pathology, and Rheumatology, Guy's & St Thomas' National Health Service (NHS) Foundation Trust, London, United Kingdom; ¹³University Children's Hospital, Basel, Switzerland; ¹⁴Obstetric Anaesthesia, St James' University Hospital, Leeds, United Kingdom; ¹⁵The Scripps Research Institute, La Jolla, CA; ¹⁶Department of Cell Therapy and Hematology, San Bortolo Hospital, Vicenza, Italy; ¹⁷Department of Haematology, Hospital Universitario La Fe, Valencia, Spain; ¹⁸Comprehensive Bleeding Disorders Center, Peoria, IL; ¹⁹ITP Support Association, Bedford, United Kingdom; ²⁰Platelet Disorder Support Association, Rockville, MD; and ²¹Department of Hematology, Massachusetts General Hospital and Harvard Medical School, Boston

Previously published guidelines for the diagnosis and management of primary immune thrombocytopenia (ITP) require updating largely due to the introduction of new classes of therapeutic agents, and a greater understanding of the disease pathophysiology. However, treatment-

related decisions still remain principally dependent on clinical expertise or patient preference rather than high-quality clinical trial evidence. This consensus document aims to report on new data and provide consensus-based recommendations relating to diagnosis and treatment

of ITP in adults, in children, and during pregnancy. The inclusion of summary tables within this document, supported by information tables in the online appendices, is intended to aid in clinical decision making. (Blood. 2010;115:168-186)

Introduction

Primary immune thrombocytopenia (ITP) is an acquired immune-mediated disorder characterized by isolated thrombocytopenia, defined as a peripheral blood platelet count less than $100 \times 10^9/L$, and the absence of any obvious initiating and/or underlying cause of the thrombocytopenia.¹ Until recently, the abbreviation ITP stood for idiopathic thrombocytopenic purpura, but current awareness relating to the immune-mediated nature of the disease, and the absence or minimal signs of bleeding in a large proportion of cases have led to a revision of the terminology.¹ Concepts surrounding the mechanisms of thrombocytopenia in ITP have shifted from the traditional view of increased platelet destruction mediated by autoantibodies to more complex mechanisms in which both impaired platelet production and T cell-mediated effects play a role.²⁻⁶ Recent epidemiologic data suggest that the incidence in adults is approximately equal for the sexes except in the mid-adult years (30-60 years), when the disease is more prevalent in women.^{7,8} ITP is classified by duration into newly diagnosed, persistent (3-12 months' duration) and chronic (≥ 12 months' duration).¹ Whereas ITP in adults typically has an insidious onset with no preceding viral or other illness and it normally follows a chronic course,⁹ ITP in children is usually short-lived with at least two-thirds recovering spontaneously within 6 months.¹⁰ Signs and symptoms vary widely. Many patients have either no symptoms or

minimal bruising, whereas others experience serious bleeding, which may include gastrointestinal hemorrhage (GI), extensive skin and mucosal hemorrhage, or intracranial hemorrhage (ICH). The severity of thrombocytopenia correlates to some extent but not completely with the bleeding risk.^{7,11} Additional factors (eg, age, lifestyle factors, uremia) affect the risk and should be evaluated before the appropriate management is determined.

The investigation and management of ITP patients vary widely. The purpose of this consensus document is to comment on new data and provide recommendations relating to diagnosis and treatment. Final judgment regarding care of individual patients should, however, lie with the responsible health care professional and be based on careful investigation of individual circumstances.

Methods

Composition of the panel. The panel included 22 members with recognized clinical and research expertise in ITP representing North America (United States, 7; Canada, 1), Europe (France, 1; Italy, 2; Spain, 1; Switzerland, 1; United Kingdom, 8), and Australia (1).

Assessment of the literature. Articles were identified by a computer-assisted search of the literature published in English using the National Library of Medicine PubMed database. The

Table 1. Recommendations for the diagnosis of ITP in children and adults

Basic evaluation	Tests of potential utility in the management of an ITP patient	Tests of unproven or uncertain benefit
<ul style="list-style-type: none"> • Patient history • Family history • Physical examination • Complete blood count and reticulocyte count • Peripheral blood film • Quantitative immunoglobulin level measurement† • Bone marrow examination (in selected patients; refer to text) • Blood group (Rh) • Direct antiglobulin test • <i>H pylori</i>† • HIV† • HCV† 	<ul style="list-style-type: none"> • Glycoprotein-specific antibody • Antiphospholipid antibodies (including anticardiolipin and lupus anticoagulant) • Antithyroid antibodies and thyroid function • Pregnancy test in women of childbearing potential • Antinuclear antibodies • Viral PCR for parvovirus and CMV 	<ul style="list-style-type: none"> • TPO • Reticulated platelets • PaltG • Platelet survival study • Bleeding time • Serum complement

Refer also to supplemental Document 2.

Rh indicates rhesus; *H pylori*, *Helicobacter pylori*; HIV, human immunodeficiency virus; HCV, hepatitis C virus; PCR, polymerase chain reaction; CMV, cytomegalovirus; TPO, thrombopoietin; and PaltG, platelet-associated immunoglobulin G.

*Quantitative immunoglobulin level measurement should be considered in children with ITP and is recommended in those children with persistent or chronic ITP as part of the reassessment evaluation.

†Recommended by the majority of the panel for adult patients regardless of geographic locale.

search criteria were: ‘immune thrombocytopenic purpura’, ‘idiopathic thrombocytopenic purpura’, ‘ITP’, and ‘autoimmune thrombocytopenic purpura’. A subsequent search was performed using the corresponding MedLine MeSH terms and cross-referenced with the original search to consolidate the primary results. Abstracts from the European Haematology Association (EHA), American Society of Hematology (ASH), and International Society on Thrombosis and Haemostasis (ISTH) annual meetings from 2003 to 2007 were also reviewed for relevance. Papers were graded using a specific scoring system (supplemental Document 1). Levels of evidence were reviewed by the lead writing committee at 2 face-to-face meetings throughout the manuscript preparation, and all authors were given the chance to dispute the levels assigned at each review stage. Randomized controlled trials (RCTs) were graded as providing the highest level of evidence, with case studies and expert opinion the lowest. Grades of recommendation were based on the supporting evidence levels.

The relevant data are presented in the text with additional supporting tables and appendices available on the *Blood* website (see the Supplemental Materials link at the top of the online article).

Diagnostic approach in patients with suspected ITP

Diagnostic tools for adults and children with suspected ITP were grouped into 3 sections of recommendation (supplemental Document 8, Recommendation Box 1; Table 1). A presumptive diagnosis of ITP is made when the history, physical examination, complete blood count, and examination of the peripheral blood smear do not suggest other etiologies for the thrombocytopenia. There is no “gold standard” test that can reliably establish the diagnosis. Response to ITP-specific therapy, for example, intravenous immunoglobulin (IVIg) and intravenous anti-D, is supportive of the diagnosis, but a response does not exclude secondary ITP.

Patient history

Thrombocytopenia can be caused by myriad conditions including systemic disease, infection, drugs, and primary hematologic disorders

(Table 2). In approximately 60% of pediatric cases, there is a history of a previous infection.¹² An increased risk of ITP is also associated with measles-mumps-rubella vaccination.¹³ Bleeding after previous surgery, dentistry, and trauma should be considered when estimating the possible duration of chronic thrombocytopenia or an alternative bleeding disorder. If a diagnosis of ITP is established, contraindications to or cautions about corticosteroid therapy should be noted. Inherited thrombocytopenia should be considered in patients with long-standing thrombocytopenia unaffected by treatment and in those with a family history of thrombocytopenia or bleeding disorders.

The possibility of abuse must be considered by emergency department staff when dealing with a young child who presents with bruising and purpura for the first time (evidence level IV). Children with infections such as meningococcal sepsis usually have other systemic features that help rapidly differentiate such conditions from ITP.

Table 2. Frequent examples of differential diagnosis of ITP and potential alternative causes of thrombocytopenia identified by patient history

- Previously diagnosed or possible high risk of conditions that may be associated with autoimmune thrombocytopenia, for example, HIV, HCV, or other infection; other autoimmune/immunodeficiency disorders (including systemic lupus erythematosus [SLE]); malignancy (eg, lymphoproliferative disorders); recent vaccination
- Liver disease (including alcoholic liver cirrhosis)
- Drugs (prescription or non-prescription), alcohol abuse, consumption of quinine (tonic water), exposure to environmental toxins
- Bone marrow diseases including myelodysplastic syndromes, leukemias, other malignancies, and fibrosis, aplastic anemia, and megaloblastic anemia
- Recent transfusions (possibility of posttransfusion purpura) and recent immunizations
- Inherited thrombocytopenia: thrombocytopenia-absent radius (TAR) syndrome, radioulnar synostosis, congenital amegakaryocytic thrombocytopenia, Wiskott-Aldrich syndrome, MYH9-related disease, Bernard-Soulier syndrome, type IIB von Willebrand disease

Refer also to supplemental Document 2.

Physical examination

Physical examination should be normal aside from bleeding manifestations. Mild splenomegaly may be found in younger patients, but moderate or massive splenomegaly suggests an alternative cause. Constitutional symptoms, such as fever or weight loss, hepatomegaly, or lymphadenopathy might indicate underlying disorder such as HIV, systemic lupus erythematosus (SLE), or a lymphoproliferative disease.

Peripheral blood count

ITP is characterized by isolated thrombocytopenia with an otherwise normal complete blood count. Anemia from blood loss may be present, but it should be proportional to the amount, and the duration, of bleeding and may result in iron deficiency (evidence level IV). If anemia is found, the reticulocyte count may help define whether it the result of poor production or increased destruction of red blood cells (RBCs).

Evaluation of peripheral blood smear

Evaluation of the peripheral blood smear by a qualified hematologist or pathologist is paramount to the diagnosis of ITP. This may demonstrate abnormalities that are not consistent with ITP, such as schistocytes in patients with thrombotic thrombocytopenic purpura–hemolytic uremic syndrome, or leukocyte inclusion bodies in MYH9-related disease. Excessive numbers of giant or small platelets may indicate an inherited thrombocytopenia (supplemental Document 9). Pseudo-thrombocytopenia due to ethylenediaminetetra acetic acid (EDTA)–dependent platelet agglutination should also be excluded¹⁴ (evidence level III).

Bone marrow examination

Bone marrow examination may be informative in patients older than 60 years of age, in those with systemic symptoms or abnormal signs, or in some cases in which splenectomy is considered.^{15–18} Both a bone marrow aspirate and a biopsy should be performed. In addition to the morphologic assessment, flow cytometry and cytogenetic testing should be considered (evidence level IIb–IV). Flow cytometry may be particularly helpful in identifying patients with ITP secondary to chronic lymphocytic leukemia (CLL).¹⁹

Helicobacter pylori testing

The detection of *H pylori* infection, preferably with the urea breath test or the stool antigen test, should be considered in the work-up of adults with typical ITP where it may have clinical impact²⁰ (evidence level IIa). Serologic detection may be used but is less sensitive and less specific than the other tests; furthermore, the test may produce false positive results after IVIg therapy. Except in high-prevalence areas, the literature does not support routine testing in children with ITP.

HIV and HCV testing

The thrombocytopenia associated with HIV and hepatitis C virus (HCV) infections may be clinically indistinguishable from primary ITP and can occur several years before patients develop other symptoms.²¹ Routine serologic evaluation for HIV and/or HCV infection in adult patients with suspected ITP, regardless of local background prevalence and personal risk factors documented in the patient history, is recommended. Control of these infections may result in complete hematologic remission (evidence level IIa).²¹

Quantitative immunoglobulin level testing

Baseline immunoglobulin (Ig) levels (IgG, IgA, and IgM) should be measured in adults (evidence level IV). They should also be considered at baseline in children with ITP, and measured in those children with persistent or chronic ITP as part of a reassessment evaluation. Low levels may reveal conditions such as common variable immunodeficiency (CVID) or selective IgA deficiency. Treatment of ITP with immunosuppressive agents is therefore relatively contraindicated in CVID. Although Ig levels should ideally be tested prior to use of IVIg, it will often be necessary to treat the patient before the results are known (evidence level IV).

Direct antiglobulin test

A positive direct antiglobulin test (DAT) was found in 22% of 205 patients (19 children, 186 adults) with ITP,²² but its clinical significance is unknown. A DAT is generally appropriate if anemia associated with a high reticulocyte count is found and if treatment with anti-D immunoglobulin is being considered.

Blood group Rh(D) typing

This is important if anti-D immunoglobulin is being considered.

Tests of potential utility

Antiplatelet antibody assays: glycoprotein-specific antibody testing.

Assays for antibodies to specific platelet glycoproteins are not routinely recommended because platelet-associated IgG (PAIgG) is elevated in both immune and non-immune thrombocytopenia (evidence level IV).^{23,24}

Antiphospholipid antibodies. Antiphospholipid antibodies (APLA), including anticardiolipin antibodies and lupus anticoagulant, can be found in approximately 40% of otherwise typical adult patients with ITP.²⁵ The presence of APLA does not appear to affect the response to ITP treatment. Routine testing is not recommended in the absence of symptoms of antiphospholipid syndrome.

Antinuclear antibodies. A positive antinuclear antibody (ANA) test may be a predictor of chronicity in childhood ITP²⁶ (evidence level IIb).

Antithyroid antibody and thyroid function testing. Eight percent to 14% of ITP patients followed longitudinally developed clinical hyperthyroidism.²⁷ Others developed antibodies to thyroglobulin and may eventually develop hyper- or hypothyroidism. Mild thrombocytopenia has been reported in patients with hyperthyroidism (reduced platelet survival) and hypothyroidism (possible decreased platelet production), which often resolve with restoration of the euthyroid state. It may also be useful to measure antibodies to thyroglobulin and thyroid-stimulating hormone (TSH) to identify patients at risk for clinical thyroid disease.

Testing for other acute and persistent infections. Acute viral infections and some vaccinations (with live attenuated virus) have been associated with thrombocytopenia, which is usually transient. Some chronic infections, for example, parvovirus and cytomegalovirus (CMV), can also produce thrombocytopenia.

Diagnostic tests of unproven or uncertain benefit

Several other tests (Table 1) currently have no proven role in the differential diagnosis of ITP from other thrombocytopenias and do not guide patient management.

Table 3. Therapies for the treatment of ITP

Clinical situation	Therapy option
First line (initial treatment for newly diagnosed ITP)	Anti-D Corticosteroids: dexamethasone, methylprednisolone, prednis(ol)one IVIg
Second line	Azathioprine Cyclosporin A Cyclophosphamide Danazol Dapsone Mycophenolate mofetil Rituximab Splenectomy TPO receptor agonists Vinca alkaloids
Treatment for patients failing first- and second-line therapies	Category A: treatment options with sufficient data TPO receptor agonists Category B: treatment options with minimal data and considered to have potential for considerable toxicity Campath-1H Combination of first- and second-line therapies Combination chemotherapy HSCT

Treatment options for ITP are listed in alphabetical order and thus do not imply a preferred treatment option.

HSCT indicates hematopoietic stem cell transplantation; TPO, thrombopoietin; and IVIg, intravenous immunoglobulin.

Management of adult ITP

Although RCT data are now available for some new ITP treatments (eg, romiplostim, eltrombopag), only a limited number of RCTs have been conducted in adults using traditional therapies and even fewer for other agents. Whereas this document gives a widespread approach to treatment (Table 3), a general rule is that treatment should always be tailored to the individual patient. All treatment options are listed alphabetically so as to show no preference for a particular therapy. Response rate criteria vary between studies, making direct comparisons of response rates given for individual treatment options difficult.

Due to the costs of modern drug development, newer therapies may be expensive, which could potentially limit their availability and use in some countries. Financial resources, either of the individual patient or of the publicly funded health care system, may also strongly impact the choice of treatment. However, this higher cost needs to be offset by the fact that these new agents are not immunosuppressive, have undergone rigorous randomized controlled clinical studies, and appear to have high efficacy.

Who should be treated?

Relevant factors that contribute to management decisions include the extent of bleeding, comorbidities predisposing to bleeding, complications of specific therapies, activity and lifestyle, tolerance of side effects, potential interventions that may cause bleeding, accessibility of care, patient expectations, patient worry or anxiety about disease burden, and patient need for non-ITP medications that may create a bleeding risk.

Although hemorrhagic death is a major concern, analysis of data from 17 adult case studies estimated the rate of fatal hemor-

rhage to be 0.0162 to 0.0389 cases per adult patient-year at risk.²⁸ Patients older than 60 years and those with previous hemorrhage have a higher bleeding risk.²⁹ Bleeding and infection contribute equally to mortality.³⁰

Treatment is rarely indicated in patients with platelet counts above $50 \times 10^9/L$ in the absence of the following: bleeding due to platelet dysfunction or another hemostatic defect, trauma, surgery,³¹ clearly identified comorbidities for bleeding, mandated anticoagulation therapy, or in persons whose profession or lifestyle predisposes them to trauma. Patient preference must also be considered when discussing treatment options. Detailed consensus-based recommendations regarding target platelet counts during surgery in adults were provided previously¹⁶ and have been further modified (supplemental Document 8, Recommendation Box 2).

First-line treatment: initial treatment for newly diagnosed patients

Response rate criteria vary between studies (supplemental Document 8, Recommendation Box 3) and it is not possible to compare response rates for individual treatment options.

Corticosteroid therapy. Corticosteroids are the standard initial treatment. Additionally, they may also reduce bleeding, independent of the platelet count rise by means of a direct effect on blood vessels.^{32,33} Unfortunately their adverse effects rapidly become apparent and create significant complications. With time, the detrimental effects of corticosteroids often outweigh their benefits. Prednisone is the standard initial first-line therapy for ITP patients.^{22,34,35} Prednisone is usually given at 0.5 to 2 mg/kg/d until the platelet count increases ($\geq 30-50 \times 10^9/L$), which may require several days to several weeks.^{9,36,37} Although the treatment is effective, patients are at risk of developing corticosteroid-related complications that vary with the dose and duration. To avoid corticosteroid-related complications, prednisone should be rapidly tapered and usually stopped in responders, and especially in non-responders after 4 weeks.^{36,38}

Dexamethasone. Although it has been abandoned in the treatment of chronic refractory ITP patients,^{39,40} recent results from 2 large first-line studies with dexamethasone suggest both a high initial response rate and a substantial sustained response rate (Table 4). Administration of dexamethasone 40 mg/day for 4 days (equivalent to ~ 400 mg of prednisone per day) produced sustained response in 50% of newly diagnosed adults with ITP. In another study, 4 cycles of dexamethasone (40 mg/day for 4 days) given every 14 days produced an 86% response rate with 74% having responses lasting a median time of 8 months.⁴¹ RCTs are needed to definitively assess these encouraging results and to distinguish whether pulse dexamethasone is the preferred corticosteroid approach with regard to response, duration of response, and toxicity.

Methylprednisolone. Parenteral administration of high-dose methylprednisolone has been used in various regimens to treat patients failing first-line therapies,^{42,43} with 80% response rates. Due to the short-term responses to methylprednisolone, maintenance therapy with oral corticosteroids may be required (evidence level IV).

Intravenous anti-D (IV anti-D). IV anti-D is appropriate for Rh(D) positive, non-splenectomized ITP patients. It should be avoided in those with autoimmune hemolytic anemia, to avoid exacerbation of hemolysis. Blood group, DAT, and reticulocyte count are required before treating with IV anti-D.^{44,45}

IV anti-D may be an effective alternative to IVIg, as it can be infused in a shorter time, is produced from a smaller donor pool, has a potentially longer response,^{46,47} and may reduce the need for

Table 4. First-line treatment options for adult ITP patients

Recommended treatment strategy	Approximate response rate	Approximate time to response	Toxicities	Duration of sustained response
Corticosteroids				
Dexamethasone 40 mg daily for 4 d every 2-4 wk for 1-4 cycles	Up to 90% of patients respond initially	Several days to several weeks	Vary with length of administration: mood swings, weight gain, anger, anxiety, insomnia, Cushingoid faces, dorsal fat, diabetes, fluid retention, osteoporosis, skin changes including thinning, alopecia, hypertension, GI distress and ulcers, avascular necrosis, immunosuppression, psychosis, cataracts, opportunistic infections, adrenal insufficiency; hypertension, anxiety. Tolerability decreases with repeated dosing. Possibly lower rate of adverse events when used as short-term bolus therapy	As high as 50%-80% reported, the latter with 3-6 cycles (during 2-5 y of follow-up)
Methylprednisolone 30 mg/kg/d for 7 d	As high as 95%	4.7 d vs 8.4 d (high-dose methylprednisolone [HDMP] vs prednisone)		23% of patients have sustained platelet count ($> 50 \times 10^9/L$) at 39 mo
Prednis(ol)one 0.5-2 mg/kg/d for 2-4 wk	70%-80% of patients respond initially	Several days to several weeks		Remains uncertain; estimated 10-y disease-free survival 13%-15%
IV anti-D				
50-75 $\mu g/kg$	Initial response rate similar to IVIg (dose dependent)	4-5 d	Common: hemolytic anemia (dose-limiting toxicity), fever/chills Rare: intravascular hemolysis, disseminated intravascular coagulation, renal failure, rare death	Typically last 3-4 wk but may persist for months in some patients
IVIg*				
0.4 g/kg/d for 5 d or infusions of 1 g/kg/d for 1-2 d	Up to 80% of patients respond initially; half achieve normal platelet counts	Rapid; many respond in 24 h; typically 2-4 d	Headaches common: often moderate but sometimes severe Transient neutropenia, renal insufficiency, aseptic meningitis, thrombosis, flushing, fever, chills, fatigue, nausea, diarrhea, blood pressure changes and tachycardia IVIg preparations may contain small quantities of IgA, which occasionally causes anaphylactoid reactions in patients with IgA deficiency; in these cases use IgA-depleted IVIg	Usually transient; platelet counts returning to pretreatment levels 2-4 wk after treatment; persists for months in a few patients

Full details regarding the studies found in the literature search are available in supplemental Document 3.

*IVIg may be discontinued after 1 to 2 days if adequate response is seen.

splenectomy.⁴⁸⁻⁵⁰ Two studies have demonstrated that IV anti-D administered at 75 $\mu g/kg$, instead of the licensed 50 $\mu g/kg$ dose, increases the overall platelet count comparable to that of IVIg.^{51,52} Premedication with paracetamol/acetaminophen, or corticosteroids (eg, 20 mg of prednisone), is recommended to reduce the risk of fever/chill reactions especially with the higher dose.⁵¹ Mild anemia is expected and may be dose-limiting.⁴⁸ Rare, but very serious, even fatal, cases of intravascular hemolysis, disseminated intravascular coagulation, and renal failure have been reported^{44,45,53} (evidence level Ib-III). IV anti-D is a pooled, biological blood product, the risks of which must be explained to patients. Recent safety concerns have been raised regarding the product WinRho SDF that has prompted its removal from the European market. Until the full nature of these adverse effects is assessed, this agent should be used with caution. A more convenient⁵⁴⁻⁵⁷ and perhaps more tolerable^{56,57} delivery of anti-D immune globulin by the intramuscular^{54,55} or subcutaneous^{56,57} route has been reported in limited, open-label trials of adults⁵⁴ and children⁵⁵⁻⁵⁷ with chronic ITP. In all, the majority of patients exhibited a platelet response within 1 week of treatment, with no reports of severe adverse events. Controlled prospective trials are needed to place subcutaneous or intramuscular anti-D among recommended therapies for ITP.

IVIg. Numerous controlled trials have been performed with high-dose IVIg since its initial use approximately 20 years ago⁵⁸ and have shown initial response rates comparable to those of corticosteroids but with a shorter time to response.¹⁶ ITP patients with CVID may be treated with high-dose IVIg followed by maintenance dosing of 0.3 to 0.4 g/kg every 3 to 4 weeks.⁵⁹

Although IVIg is associated with higher toxicity, especially headaches, and the need for a prolonged infusion (over at least several hours), IVIg recipients are more likely to attain a platelet increase within 24 hours at a dose of 1 g/kg (1-2 infusions over 2 days) compared with the historical treatment regimen (0.4 g/kg/d

over 5 days).⁶⁰ Rare but serious toxicities include renal failure and thrombosis.^{61,62} The fear of transmission of infectious disease persists, but there is no recent evidence for transmission of HIV, HCV, and HBV, and human T-cell lymphotropic virus type 1 (HTLV-1). It appears that in some patients corticosteroids may enhance the IVIg response. In addition to this, the concomitant use of corticosteroids may reduce infusion reactions and prevent aseptic meningitis.

Emergency treatments

An urgent increase in platelet count may be required for some thrombocytopenic patients needing surgical procedures, at high risk of bleeding, or with active central nervous system (CNS), GI, or genitourinary bleeding (supplemental Document 8, Recommendation Box 4).

Although changing from corticosteroids to IVIg or anti-D may be effective in emergency settings, combining first-line therapies is appropriate: prednisone and IVIg are recommended for the emergency treatment of patients with uncontrolled bleeding. High-dose methylprednisolone (HDMP) may also be useful in this setting. Other therapies that work rapidly include platelet transfusion, possibly in combination with IVIg, and emergency splenectomy.⁶³ There is also some evidence of rapid response to vinca alkaloids.

General measures. These include cessation of drugs reducing platelet function, control of blood pressure, inhibition of menses, and efforts to minimize trauma (evidence level IV). However, there may be instances in which oral anti-coagulation or antiplatelet medication is necessary (eg, in patients with cardiac stents requiring aspirin and/or clopidogrel) and necessitates raising the threshold platelet count for treatment. In patients with reduced renal

Table 5. Second-line treatment options for adult ITP patients

Recommended treatment strategy	Approximate response rate	Approximate time to response	Toxicities	Duration of sustained response
Azathioprine 1-2 mg/kg (maximum: 150 mg/d)	Up to two-thirds of patients; 40% in anecdotal reports	Slow; may need to be continued for 3-6 mo	Low incidence and generally mild: weakness, sweating, transaminase elevations, severe neutropenia with infection, pancreatitis	Up to a quarter of patients off therapy maintain response
Cyclosporin A 5 mg/kg/d for 6 d then 2.5-3 mg/kg/d (titration to blood levels of 100-200 ng/mL)	Dose-dependent. High response rate (~50%-80%) in small series	3-4 wk	In most patients, the following are seen to some degree; moderate but transient: increase in serum creatinine, hypertension, fatigue, paresthesias, gingival hyperplasia, myalgia, dyspepsia, hypertrichosis, tremor	More than half of responders receiving low doses sustain remission (at least 2 y)
Cyclophosphamide (1-2 mg/kg orally daily for at least 16 wk) or IV (0.3-1 g/m ² for 1-3 doses every 2-4 wk)	24%-85% of patients	1-16 wk	Most are mild to moderate: neutropenia, acute deep venous thrombosis, nausea, vomiting	Up to 50% show a sustained response
Danazol 200 mg 2-4 times daily	67% complete or partial response; 40% in anecdotal reports	3-6 mo	Frequent side effects: acne, increased facial hair, increased cholesterol, amenorrhea, transaminitis	46% remained in remission at a median of 119 ± 45 mo and mean duration of danazol therapy was 37 mo
Dapsone 75-100 mg	Response in up to 50% of patients	3 wk	Infrequent and treatable/reversible: abdominal distension, anorexia, nausea, methemoglobinuria, hemolytic anemia in those with G6PD deficiency. Severe: skin rash may require drug to be stopped	Sustained response in up to two-thirds of responders off therapy
Mycophenolate mofetil 1000 mg twice daily for at least 3-4 wk	Up to 75% of patients; complete response in up to 45%	4-6 wk	Mild and infrequent: headache (most common and dose-limiting), backache, abdominal distension, anorexia, nausea	Sustained for short time after treatment discontinuation
Rituximab 375 mg/m ² weekly ×4 (lower doses may also be effective)	60% of patients; complete response in 40% of patients	1-8 wk	Low rate, usually mild-to-moderate first-infusion fever/chills, rash, or scratchiness in throat. More severe reactions include serum sickness and (very rarely) bronchospasm, anaphylaxis, pulmonary embolism, retinal artery thrombosis, infection, and development of fulminant hepatitis via reactivation of hepatitis B. Rare cases of progressive multifocal leukoencephalopathy.	Sustained response > 3-5 y in 15%-20% of responders. Responders may require retreatment months to years later
Splenectomy	80% of patients respond; approximately two-thirds achieve a lasting response	1-24 d	Hemorrhage, peripancreatic hematoma, subphrenic abscess, wound infection, death, pneumococcal infection, fever, overwhelming sepsis syndrome, thrombosis	Response sustained with no additional therapy in approximately two-thirds of patients over 5-10 y
TPO receptor agonist: eltrombopag 25-75 mg orally daily	Platelet responses (platelet count > 50 × 10 ⁹ /L on d 43 of study): 70% receiving 50-mg dose, 81% receiving 75-mg dose	By d 15, more than 80% of patients receiving 50 or 75 mg of eltrombopag daily increased platelet count	Adverse events in at least 20% of patients: headache. Treatment-related serious adverse events: increased bone marrow reticulins, worsening thrombocytopenia upon discontinuation, thrombosis, liver function abnormalities in 13%	Up to 1.5 y with continual administration of the drug
TPO receptor agonist: romiplostim. Doses 1-10 µg/kg subcutaneously weekly	Overall platelet response rate: non-splenectomized, 88%; splenectomized, 79%	1-4 wk (in patients with platelet count < 30 × 10 ⁹ /L to achieve > 50 × 10 ⁹ /L)	Adverse events in at least 20% of patients: headache, fatigue, epistaxis, arthralgia and contusion (similar incidence in placebo groups). Treatment-related serious adverse events: increased bone marrow reticulins, worsening thrombocytopenia upon discontinuation, thrombosis	Up to 4 y with continual administration of the drug
Vinca alkaloid regimens: vincristine total dose of 6 mg (1-2 mg per infusion weekly); vinblastine total dose of 30 mg (10 mg per infusion weekly), and some patients, vincristine and vinblastine infusions administered alternately	Highly variable transient response in 10%-75% of patients	5-7 d	Neuropathy especially with repeated dose and in the elderly; neutropenia, fever, inflammation/thrombophlebitis at the infusion site	A normal platelet count was observed in 6 of 9 (9/12 had response) patients under long-term 3-36 mo monitoring; average, 10 mo

Further details regarding the studies found in the literature search (2001-2008) are available in supplemental Document 3. Long-term responses for many of these agents are based on fragmented data and potentially poor follow-up.

function, hemostasis may be improved with **desmopressin** and by **maintaining hemoglobin at a minimum of 10 g/dL**.

Platelet transfusions with or without IVIg. Platelet transfusion increases the posttransfusion platelet count by more than 20 × 10⁹/L in 42% of bleeding ITP patients and may reduce bleeding.⁶⁴ In a retrospective study of 40 patients⁶³ (evidence level IIB), **concurrent administration of platelet transfusions and IVIg was associated with resolution of bleeding, rapid restoration of adequate platelet counts, and minimal side effects** (evidence level III/IV).

Vinca alkaloids. As a single agent, vincristine induces a platelet count increase in a small fraction of chronic ITP patients (evidence level IV). However, when combined with other agents it may be a useful approach in patients requiring emergency treatment⁶⁵ (evidence level IIB).

Emergency splenectomy. See “Splenectomy” in “Second-line therapy: surgical.”

Antifibrinolytics. Antifibrinolytic agents, such as oral or IV **tranexamic acid** and epsilon-aminocaproic acid may be useful in preventing recurrent bleeding in patients with severe thrombocytopenia; however, the efficacy has not been evaluated by randomized trial in ITP patients. Tranexamic acid (1 g, 3 times daily orally) and epsilon-aminocaproic acid (1-4 g every 4-6 hours [maximum dose, 24 g/d]) may be of special value in certain dental or surgical procedures.

Emergency treatments that are not indicated

Plasmapheresis. Plasmapheresis has been studied in small cohorts of ITP patients, some of whom had acute ITP. No patients with chronic ITP showed a response⁶⁶ (evidence level III).

Second-line treatment options for adult ITP patients

Splenectomy and a large number of drugs have been used as second-line therapy with variable success. Physicians are required to make individual judgments about the nature of second-line treatment based on bleeding history, comorbidities, patient expectations, and compliance.

The main goal of second-line therapy is to attain a sustained increase of the platelet count that is considered hemostatic for the individual patient. Available treatment modalities have quite different mechanisms of action and can be broadly categorized into those that are given only once (or for only one course) and are intended to induce long-term remission (splenectomy, rituximab), and those that need continued or chronic administration (corticosteroids, immunosuppressive agents, thrombopoietin receptor agonists).

Depending on the clinical setting, splenectomy is deferred in most patients for at least 6 months. This may be due to patient preference or other active comorbidities and to the understanding that spontaneous improvement or late remission may occur 6 to

12 months after diagnosis; indeed, some patients may spontaneously remit even years after diagnosis.

Second-line therapy: medical. Treatment options are listed alphabetically so as to show no preference for a particular therapy (supplemental Document 8, Recommendation Box 5; Table 5).

Azathioprine. Despite few new data, consensus was that this agent is still useful. Investigators have reported complete responses in 45% of 53 patients (40 splenectomized) treated with azathioprine (150 mg/day) for a median of 18 months.⁶⁷ Although continued therapy is generally required, often a reduced dose suffices. Leukemia has only rarely been associated with azathioprine in other disorders but has not been described in ITP patients⁶⁸ (evidence level III).

Cyclosporin A. Cyclosporin A (2.5-3 mg/kg/d) is effective as a single agent in ITP patients or when given with prednisone, but its side effects may make it unsuitable for some patients (eg, older patients and those with renal insufficiency). Clinical improvement was observed in more than 80% of patients resistant to first-line therapy, with 42% achieving a complete response⁶⁹ (evidence level IIa). Remissions may be durable (mean, 29 months) following discontinuation of treatment⁷⁰ (evidence level IIb). Side effects are usually moderate but transient and include fatigue, renal insufficiency, hypertension, and neuropathy.⁶⁹

Cyclophosphamide. Immunosuppression with cyclophosphamide, either orally (1-2 mg/kg daily for at least 16 weeks) or intravenously (0.3-1 g/m² for 1-3 doses every 2-4 weeks), has been used for patients refractory to corticosteroids and/or splenectomy. Response rates varied from 24% to 85%^{43,71,72} and toxicity was mild to moderate.⁷² However, there are reports of ITP and SLE patients developing acute myeloid leukemia (AML) after cyclophosphamide therapy.⁷³ The complication of sterility after treatment for ITP has not been adequately addressed.

Danazol. Danazol is an attenuated androgen administered orally at a dose of 200 mg, 2 to 4 times daily (10-15 mg/kg/d). Response rates of 60% to 67% have been recorded ($> 50 \times 10^9/L$ for ≥ 2 months in 57 ITP patients after splenectomy).⁷⁴ Older females and splenectomized patients may have the highest rate of response.⁷⁴

Dapsone. Dapsone is a moderate corticosteroid-sparing agent that is usually administered orally at a dose of 75 to 100 mg/d.⁷⁵ Dapsone may delay splenectomy for up to 32 months in patients who have not responded to first-line corticosteroid therapy (evidence level IIb). However, splenectomized patients have a low response rate.⁷⁶

Male patients at risk for glucose-6-phosphate dehydrogenase (G6PD) deficiency should be screened before starting treatment and monitored for hemolysis and methemoglobinemia⁷⁷ (evidence level III).

Mycophenolate mofetil. Mycophenolate mofetil (MMF), an antiproliferative immunosuppressant, has been shown to be useful in some ITP patients. Administration of MMF at progressively increasing doses (250 mg up to optimally 1000 mg/day twice a week over 3 weeks) produced platelet increase in 39% of patients with refractory ITP, but was not sustained⁷⁸ (evidence level IIb). In a retrospective study, the overall response rate was 78% (major response, $> 80 \times 10^9/L$; and moderate response, $30-80 \times 10^9/L$ at 3 months).⁷⁹

Rituximab. Several publications have reported the use of rituximab in ITP patients since previous consensus documents were issued^{15,16} and suggest that about 60% of patients respond, with approximately 40% achieving complete response.⁸⁰ Responses generally occur after 1 to 2 weeks to 6 to 8 weeks^{81,82} and last from

2 months in partial responders to 5 years or longer in 15% to 20% of initially treated patients.⁸⁰ Most patients with a durable (> 1 year) complete response will respond to repeat treatment if they relapse (evidence level IIa-III).

After 2 years of observation in a prospective, open-label, single-arm phase 2 trial, 33% of patients had a platelet count of $50 \times 10^9/L$ or higher and 40% had a platelet count of $30 \times 10^9/L$ or higher without any additional treatment.⁸³ Although the studies presented used rituximab doses of 375 mg/m², lower doses (100 mg IV weekly for 4 weeks) may also be effective, although associated with a longer time to response.⁸⁴ At the current time the standard dose of rituximab for ITP patients is unknown, and, due to the potential toxicity and expense of the agent, future studies are required to identify the optimal dose. High response rates have recently been reported for a combination of rituximab with high-dose dexamethasone as initial therapy.⁸⁵

Rituximab is contraindicated in patients with evidence of active hepatitis B infection (eg, positive hepatitis B/C core antibody). Adverse events associated with rituximab are usually mild or moderate, with a low incidence of infections.^{82,86} There are also reports of more than 50 cases of progressive multifocal leukoencephalopathy associated with rituximab treatment in patients with lymphoma and more recently a limited number of patients with SLE and ITP.^{87,88} Hence, additional long-term safety data are required. These cases tend to occur in patients who are heavily immunosuppressed and on combination treatments.

Thrombopoietin-receptor agonists: romiplostim and eltrombopag. Rather than modulating the immune system, another therapeutic approach is to stimulate platelet production. Thrombopoietin (TPO) is the primary factor regulating platelet production,⁸⁹ and several TPO-receptor agonists have been developed that activate the TPO receptor and increase platelet production.⁹⁰⁻⁹³ Two agents, romiplostim and eltrombopag, are FDA-approved for the treatment of ITP. Romiplostim is administered as a 1 to 10 $\mu g/kg$ subcutaneous weekly injection.^{93,94} Eltrombopag is an oral non-peptide TPO-receptor agonist administered as a 25, 50, or 75 mg daily dose^{92,94,95} (evidence level Ib/IIa).

Data from phase 1-3 trials have demonstrated that both drugs are highly effective in increasing the platelet count in both healthy volunteers and ITP patients.^{90,92-98} In 2 parallel, placebo-controlled, double-blind randomized phase 3 trials, romiplostim was given to 63 splenectomized and 62 non-splenectomized patients for 6 months.⁹³ An overall platelet response rate (≥ 4 out of 24 study weeks $> 50 \times 10^9/L$) was observed in 79% and 88% of romiplostim-treated patients, compared with 0% and 14% in the respective placebo arms.⁹³ Similar results have been achieved with eltrombopag in chronic relapsed or refractory ITP patients ($n = 114$); 59% of eltrombopag-treated patients compared with 16% of placebo-treated patients achieved a platelet count of $50 \times 10^9/L$ or higher on day 43 of the study.⁹⁴

Across the 2 romiplostim studies, 87% of romiplostim-treated patients reduced or discontinued concurrent ITP therapy, including corticosteroids and IVIg.⁹³ Long-term data with romiplostim showed that responses were sustained for up to 4 years on continuous therapy, with most patients able to decrease or discontinue concurrent corticosteroid therapy.⁹⁸ This is an important finding, especially as it affects patients who may have been on immunosuppressive treatment for a long period of time. TPO-receptor agonists have the potential to minimize morbidity and mortality in these patients.

Although most adverse effects were mild, concerns have been raised over the increased bone reticulin found in 10 of more

than 271 patients included in the romiplostim trials and in 7 of 117 patients in the eltrombopag trials. Long-term studies will address the importance of this finding and determine whether routine monitoring is required.^{93,98} Although reported in rodent studies with eltrombopag, there was no increase in cataracts observed in the ITP studies.^{92,94,99} Liver function test abnormalities were seen in 13% of eltrombopag-treated patients.¹⁰⁰

Due to their mechanism of action, TPO-receptor agonists are considered a maintenance therapy. Upon cessation of treatment, most patients return to lower platelet counts (~10% transiently falling below baseline platelet counts); however, a few patients are able to discontinue treatment successfully.⁹³

Vinca alkaloids. Vinca alkaloids may cause a transient platelet count increase in two-thirds of patients lasting 1 to 3 weeks.¹⁵ Approximately 50% of splenectomized patients respond to vinca alkaloids but this is not sustained.^{15,101,102}

Second-line therapy: surgical. Splenectomy. Eighty percent of patients respond to splenectomy, and response is sustained in 66% with no additional therapy for at least 5 years¹⁰³⁻¹⁰⁵ (supplemental Document 8, Recommendation Box 6). Many patients without a complete response can still expect a partial or transient response.^{15,106} Approximately 14% of patients do not respond and approximately 20% of responders relapse weeks, months, or years later¹⁰³ (evidence level IIb).

Complications of splenectomy. Complications of splenectomy include bleeding, infection, thrombosis, prolonged hospitalization, readmission to the hospital, and requirement for additional intervention.¹⁰⁴ Reported complication rates vary considerably^{30,103,104,107,108} and may be greater in patients aged 65 years or older.²⁹ In a recent systematic analysis, splenectomy complication rates were 12.9% with laparotomy and 9.6% with laparoscopy; mortality was 1.0% with laparotomy and 0.2% with laparoscopy.¹⁰⁴

Because ITP²² and splenectomy¹⁰⁹ are both associated with thromboembolic risks, ITP patients should receive appropriate postoperative thromboprophylaxis.

Predicting response to splenectomy. There is no widely accepted test predicting response to splenectomy. Response to oral corticosteroids or high-dose IVIg has a low predictive value^{110,111} (evidence level IIb). **Indium-labeled autologous platelet scanning** may be the most sensitive predictor of response to splenectomy, but here too studies vary.^{112,113} **When scanning reveals splenic platelet destruction, approximately 90% of patients respond to splenectomy.**¹¹² This test is currently limited to several research centers, but if available may be useful before splenectomy (evidence level III, grade B recommendation).

Accessory splenic tissue (evidence level III/IV). Imaging techniques show accessory splenic tissue in up to 12% of splenectomized patients and almost all is removed during surgery.¹¹⁴ In patients who relapse following an initial response to splenectomy, assessment for accessory spleen should be considered. However, in patients who never responded to initial splenectomy, response is extremely rare.^{42,115}

Prevention of infection after splenectomy. Splenectomized patients are at lifelong risk for uncontrolled infection with a poor outcome from *Streptococcus pneumoniae*, *Neisseria meningitidis*, and *Haemophilus influenzae*.^{116,117}

Patients are usually given prophylactic polyvalent **pneumococcal, meningococcal C conjugate, and H influenzae b (Hib) vaccines** at least 4 weeks before (preferably) or 2 weeks after splenectomy and revaccinated according to the country-specific recommendations (evidence level IV).^{118,119} In patients who have received rituximab in the previous 6 months, vaccinations may not be

effective. Vaccination for these patients should be readdressed once B-cell recovery has occurred.

In some studies, asplenic patients were given long-term antibiotic prophylaxis (phenoxymethylpenicillin 250-500 mg twice a day or equivalent, or erythromycin 500 mg twice a day).¹²⁰ However, the benefit of lifelong antibiotic prophylaxis is unproven^{121,122} and the risk of late infection is quite low, and therefore no consensus has been reached.¹²³

A practical policy is for splenectomized patients to have a home supply of antibiotics (eg, penicillin VK, erythromycin, or levofloxacin) for use in case of a febrile illness. Patients should be educated about the risk of postsplenectomy infection, including the need to go to the emergency department if fever higher than 101°F (38°C) occurs. In addition, cards should be carried to alert physicians that the patient is asplenic; some patients may wish to wear alert bracelets or pendants (grade C recommendation, evidence level IV).

Treatment options for adult patients failing first- and second-line therapies

Patients failing first- and second-line therapies. Approximately 20% of patients do not attain a hemostatic platelet count after splenectomy or after first- and second-line medical approaches (supplemental Document 8, Recommendation Box 7); an additional 10% to 20% of splenectomy responders eventually relapse (evidence level IV). These patients may be able to tolerate severe thrombocytopenia (ie, platelet counts as low as $10 \times 10^9/L$) relatively well with near-normal quality of life (QoL). However, some have consistent and statistically significant deficits on QoL measures, bleeding, and increased risk of death.^{28,124-126} For those who fail standard therapies and still require treatment, options are limited. In this situation, the risk of further therapy must be discussed with the patient and compared with the benefit of that therapy. In addition, other potential etiologies for thrombocytopenia should be exhaustively explored.¹²⁷ Some patients opt to live with lower platelet counts instead of undergoing toxic treatments (Table 6).

Combination chemotherapy. Combination chemotherapy may be effective for some chronic refractory ITP patients.^{65,128,129} A combination of cyclophosphamide (100-200 mg/d IV) on days 1 through 5 or 7 and prednisone (0.5-1.0 mg/kg orally daily) on days 1 through 7, combined with vincristine (1-2 mg IV) on day 1, and one of the following: azathioprine (100 mg orally daily) on days 1 through 5 or 7 or etoposide (50 mg orally daily) on days 1 through 7 has been evaluated. The overall response rate in the 31 patients was 68% including a complete response in 42%; therapy was well tolerated (evidence level IIb). Longer-term follow-up is required to assess durability of remission and the risk of secondary cancers.

Campath-1H. Campath-1H is an alternative therapeutic option for severe, refractory ITP¹³⁰; however, this drug has the potential to cause severe, possibly life-threatening, immunosuppression and usually requires prolonged antifungal, antibacterial, and antiviral prophylaxis.

Hematopoietic stem cell transplantation. Remissions have been induced in some patients with chronic refractory ITP using autologous or allogeneic hematopoietic stem cell transplantation (HSCT)¹³¹⁻¹³⁴ (evidence level IIb/III). However, potentially fatal toxicities such as neutropenic fever, cerebral hemorrhage, and septicemia may occur.¹³³ HSCT is warranted only in patients with

Table 6. Recommendations for adult patients failing first- and second-line therapies

Recommended treatment strategy	Approximate response rate	Approximate time to response	Toxicities	Sustained response
Category A: treatment options with sufficient data				
TPO--receptor agonist: eltrombopag 25-75 mg orally daily	Platelet responses (platelet count $> 50 \times 10^9/L$ on d 43 of study): 70% receiving 50-mg dose, 81% receiving 75-mg dose	By d 15, more than 80% receiving 50 or 75 mg of eltrombopag daily increased platelet count	Adverse events in at least 20% of patients: headache Treatment-related serious adverse events: increased bone marrow reticulin, worsening thrombocytopenia upon discontinuation, thrombosis, liver function abnormalities in 13%	Up to 1.5 y with continuous administration of the drug
TPO--receptor agonist: romiplostim 1-10 $\mu g/kg$ subcutaneously weekly	Overall platelet response rate: Non-splenectomized, 88% Splenectomized, 79%	1-4 wk (in patients with a platelet count $< 30 \times 10^9/L$ to achieve $> 50 \times 10^9/L$)	Adverse events in at least 20% of patients: headache, fatigue. Treatment-related serious adverse events: increased bone marrow reticulin, worsening thrombocytopenia upon discontinuation, thrombosis	Up to 4 y with continuous administration of the drug
Category B: treatment options with minimal data and considered to have potential for considerable toxicity				
Campath-1H	Initial response seen in 67% of patients	1 wk to 9 mo	Fever, rigors, chills, intracranial hemorrhage, cerebral vein thrombosis, severe intravascular hemolysis, death, infection	All but 1 patient relapsed within 24 mo
Combination chemotherapy: various regimens; see supplemental Table 3 for complete regimen details	Response seen in more than two-thirds of patients	2-3 mo	Risk of second malignancies including acute leukemia, mild nausea and vomiting, alopecia, acne, hemorrhagic cystitis, neuropathy, pancytopenia	Durable response seen in two-thirds of patients achieving CR (CR in about 40% of all patients)
HSCT	Of 14 patients, 6 achieved remission	5 wk	Frequent serious toxicities reported in peri- and posttransplantation period: infection, mucocutaneous bleeding, myelosuppression, anorexia, GVHD, and death	Long-term complete remission in one-third of patients. Late (2 y) relapses

Further details regarding the studies found in the literature search (2001-2008) are available in supplemental Document 3.
CR indicates complete response; and GVHD, graft-versus-host disease.

severe chronic refractory ITP with bleeding complications unresponsive to other modalities. However, very few long-term responses have been recorded.

TPO-receptor agonists: romiplostim and eltrombopag. TPO-receptor agonists have been studied in patients after splenectomy and show an approximately 79% overall response rate^{90,92-94,98} (evidence level Ib). TPO-receptor agonists may be a costly option, and thrombocytopenia will usually return upon cessation of treatment. However, these are the only treatments for refractory ITP that have been shown to be effective in RCTs. In view of the apparent low toxicity and good tolerability of these treatments, many patients would choose to be on them indefinitely. To date, administration of romiplostim has been continued for up to 4 years without loss of benefit or cumulative toxicity.⁹⁸

Therapies whose use is not justified

The following approaches have been reviewed and are not justified for use in ITP due to evidence affirming lack of efficacy or excessive toxicity: colchicine, interferon α , protein A immunoadsorption column, plasmapheresis as an isolated approach, vitamin C, recombinant factor VIIa.

Supportive care

Antifibrinolytics. See "Emergency treatments" (evidence level IV).

Inhibition of menstrual bleeding. Both progesterone-containing intrauterine contraceptive device and oral contraceptives can decrease the frequency and amount of menstrual bleeding¹³⁵ (evidence level IIb).

Other measures. Patient groups (such as the ITP Support Association [<http://www.itpsupport.org.uk/>], the Platelet Disorder Support Association [<http://www.pdsa.org/>], and the ITP Foundation [<http://www.itpfoundation.org/>]) offer psychological support to patients by providing relevant information about their condition, available treatments, and advice on how to live with ITP.

Thrombocytopenia in pregnancy

Presentation of thrombocytopenia during pregnancy

Platelet counts are usually lower in pregnant than in non-pregnant women.¹³² This gestational thrombocytopenia is caused by a combination of hemodilution and increased platelet activation and clearance. A decrease of approximately 10% in platelet count is typical toward the end of the third trimester. ITP is estimated to occur in 1 in 1000 to 1 in 10 000 pregnant women.¹³⁷ Women with previously diagnosed ITP may experience exacerbation or relapse.^{138,139}

A study of 119 pregnancies in 92 women with ITP found that 31% required intervention. Pregnancy is associated with a procoagulant state in preparation for the hemostatic challenge of delivery¹⁴⁰ due to increased levels of fibrinogen, factor VIII, and von Willebrand factor; suppressed fibrinolysis; and a reduction in the activity of protein S.¹⁴⁰ These changes may result in fewer bleeding symptoms and therefore a greater tolerance to ITP in pregnant compared with non-pregnant women (evidence level IV).

Diagnosis of ITP first presenting in pregnancy

Recommendations for the diagnosis and management of ITP in pregnancy are mainly based on clinical experience and expert consensus, as there are few RCTs.

The diagnosis of ITP involves the exclusion of other causes of thrombocytopenia during pregnancy. As in the non-pregnant setting, diagnostic tests are used to exclude alternative causes of thrombocytopenia (see Tables 1-2 and supplemental Document 8). The work-up of a pregnant ITP patient is essentially the same as that of a non-pregnant patient; taking into account the following additions and exceptions: gestational thrombocytopenia, preeclampsia, HELLP syndrome, DIC, folate deficiency, massive obstetrical hemorrhage, acute fatty liver, antiphospholipid antibody syndrome.

Laboratory investigations for the diagnosis of ITP in pregnancy.

Bone marrow examination is not required to make the diagnosis of ITP in pregnancy (supplemental Document 8, Recommendation Box 8). The measurement of maternal antiplatelet immunoglobulin has no value in the routine diagnosis of ITP in pregnancy.

Management of ITP in pregnancy

Optimum management of ITP in pregnancy requires collaboration among the obstetrician experienced in the management of ITP, the hematologist, the obstetric anesthetist, and the neonatologist. Treatment is largely based on the risk of maternal hemorrhage. Studies have shown that pregnancy in women with ITP can proceed safely with low hemorrhagic risk for both infants and mothers.^{138,141,142} Because platelet counts may fall in the third trimester, the frequency of platelet count measurement increases to assist in making decisions regarding delivery. The aim of peripartum treatment is to ensure that there is a satisfactory maternal platelet count for delivery.

Target platelet counts for treatment. Throughout the first 2 trimesters, treatment is initiated (1) when the patient is symptomatic, (2) when platelet counts fall below 20 to $30 \times 10^9/L$, or (3) to produce an increase in platelet count to a level considered safe for procedures. **Patients with platelet counts at 20 to $30 \times 10^9/L$ or higher do not routinely require treatment.** They should be monitored more closely as delivery approaches.¹⁴³

The lowest platelet count at which it is safe to administer spinal or epidural anesthesia remains controversial due to the theoretical risk of epidural hematoma formation and neurological damage.¹⁴⁴⁻¹⁴⁶

Obstetric anesthetists generally recommend a platelet count of at least $75 \times 10^9/L$ to allow administration of spinal or epidural anesthesia. Hematologists believe that a platelet count of at least $50 \times 10^9/L$ is adequate to allow for cesarean section.

Recommended treatment options for the management of ITP in pregnancy

Primary treatment options for maternal ITP are similar to those of other adult ITP patients (supplemental Document 8, Recommendation Box 9). **Corticosteroids and IVIg are the first-line treatments for maternal ITP.**¹⁴³ The limited evidence for the use of IV anti-D,^{147,148} splenectomy, and azathioprine¹⁴⁹⁻¹⁵¹ is presented in the subsections that follow. Vinca alkaloids, rituximab, danazol, TPO-receptor agonists, and most immunosuppressive drugs (other than azathioprine) should not be used during pregnancy because of possible teratogenicity.

First-line treatment: initial treatment for newly diagnosed patients.

Corticosteroids. Prednisone at a low dose (10 - 20 mg/d) is given initially and then adjusted to the minimum dose that produces

a hemostatically effective platelet count. Worsening of the thrombocytopenia may complicate the last weeks before delivery so tapering should not be pursued aggressively at that time. Short-term, low-dose prednisone is generally considered to be effective and safe for the mother, but corticosteroids can exacerbate hypertension, hyperglycemia, and osteoporosis and may cause excessive weight gain and psychosis. After delivery, the platelet count should be monitored and corticosteroids tapered slowly to avoid a rapid fall in platelet count and to ensure that the mother's mental state is not affected (evidence level IV).

Although prednisone is metabolized in the placenta by 11-beta-hydroxylase, high doses may have an effect on the fetus. A randomized study revealed no beneficial effect of low-dose maternal corticosteroids (1.5 mg of betamethasone orally per day) on the fetal platelet count¹⁵² (evidence level Ib).

IVIg. If corticosteroid therapy is ineffective, significant side effects occur, or a more rapid platelet increase is required, IVIg should be considered. There are no comparative trials of corticosteroids and IVIg in pregnant women; however, response rates are similar to those in non-pregnant patients. After an initial response, single IVIg infusions are well tolerated and may be repeated as needed to prevent hemorrhage and provide an adequate platelet count for delivery (evidence level IV).

IV anti-D. In non-splenectomized Rh(D)-positive patients, IV anti-D 50 to 75 $\mu g/kg$ has been shown to be effective and safe for both mother and fetus in the second and third trimesters^{147,148} (evidence level IIb). In one study of anti-D for delivery, augmentation with corticosteroids or IVIg was usually required to achieve the required platelet count of $50 \times 10^9/L$.¹⁴⁷ Although complications are uncommon, monitoring is required for neonatal jaundice, anemia, and direct antiglobulin test positivity after delivery.

Management options for maternal ITP patients failing first-line treatment. Combining first-line therapy. As with non-pregnant adults, combining first-line treatments in the refractory patient may be appropriate in the weeks before delivery (evidence level IV). HDMP (1000 mg) possibly in combination with IVIg or azathioprine has been suggested as a treatment for pregnant patients refractory to oral corticosteroids or IVIg¹⁴³ (evidence level III). Data available for azathioprine in SLE and renal transplantation show that it is safe during pregnancy¹⁴⁹⁻¹⁵¹ (evidence level III) but response is slow. Cyclosporin A has not been associated with significant toxicity to mother or fetus during pregnancy.^{153,154}

If splenectomy is necessary, it is best performed in the second trimester and may be performed laparoscopically (evidence level III), but the technique may be difficult beyond 20 weeks' gestation. Appropriate vaccination during or after pregnancy is required.

Prepregnancy counseling. It is rarely necessary to advise ITP patients against pregnancy. Counseling of ITP patients considering pregnancy should address safety of mother and fetus, outcomes of worsening maternal disease, and risks of pregnancy itself (evidence level IV).

Management of delivery. Historically, management of delivery in mothers with ITP has been dominated by concerns over the risk of severe neonatal thrombocytopenia and hemorrhage (supplemental Document 8, Recommendation Box 10). In 1976, cesarean section was recommended for all ITP patients based on a reported perinatal mortality of 12% to 21% , largely resulting from birth trauma and ICH. However, these historical data were selective and excessively pessimistic. More recent reviews suggest the neonatal mortality rate of babies born to mothers with ITP is less than 1% .¹⁴¹ Large prospective studies published in the 1990s documented an incidence of "severe" neonatal thrombocytopenia ($< 50 \times 10^9/L$)

of 8.9% to 14.7%, with ICH occurring in 0% to 1.5% of infants with neonatal thrombocytopenia.^{141,155-157} There is no evidence that cesarean section is safer for the fetus with thrombocytopenia than uncomplicated vaginal delivery (which is usually safer for the mother). Moreover, most hemorrhagic events in neonates occur 24 to 48 hours after delivery at the nadir of the platelet count. Given the difficulty predicting severe thrombocytopenia in neonates and very low risk of serious hemorrhage (evidence level III, grade B recommendation), the mode of delivery in ITP patients should be determined by purely obstetric indications.^{143,158}

Management of the neonate (of mothers with ITP). Neonatal ITP (from mothers with ITP) accounts for only 3% of all cases of thrombocytopenia at delivery.¹³⁷ In low-birth-weight neonates admitted to intensive care, thrombocytopenia develops in 18% to 35% of admissions and is most common in the smallest infants¹⁵⁹ (evidence level IIB). Fetal or neonatal platelet count cannot be reliably predicted by maternal platelet count, platelet antibody levels, or history of maternal splenectomy for ITP^{141,143,160} (evidence level III). Fetal blood sampling by cordocentesis¹⁶¹ carries a fetal mortality risk of 1% to 2% (at least as high as the risk of ICH). Scalp blood sampling in early labor to measure fetal platelet count¹⁶² is technically difficult, can cause significant hemorrhage, and commonly produces misleading platelet count results because of clotting caused by exposure to vernix or amniotic fluid.¹⁶³ Attempts to measure the fetal platelet count before delivery are not recommended (evidence level III). Procedures during labor associated with increased hemorrhagic risk to the fetus should be avoided (evidence level IV) including use of (1) fetal scalp electrodes, (2) fetal blood samples, (3) ventouse delivery, and (4) rotational forceps (evidence level IV).

After delivery, a cord blood platelet count should be determined¹⁵⁷ (level III evidence, grade C recommendation) by clean venepuncture of a cord vessel rather than by draining blood from the cord. Intramuscular injections, such as vitamin K, should be avoided until the platelet count is known. Infants with subnormal counts should be observed clinically and hematologically, as platelet counts tend to nadir between days 2 and 5 after birth. Transcranial ultrasonography should be performed on neonates with platelet counts less than $50 \times 10^9/L$ at delivery (evidence level IV). Although treatment of the neonate is rarely required, in those with clinical hemorrhage or platelet counts less than $20 \times 10^9/L$, treatment with a single dose of IVIg 1 g/kg (repeated if necessary) produces a rapid response. Life-threatening hemorrhage should be treated by platelet transfusion combined with IVIg. Severe thrombocytopenia and clinical hemorrhage in neonates are rare due to maternal ITP so when present, neonatal alloimmune thrombocytopenia should be excluded by laboratory testing.

Neonatal thrombocytopenia secondary to maternal ITP may last for months and requires long-term monitoring and occasionally a second dose of IVIg at 4 to 6 weeks after birth. In alloimmune thrombocytopenia, fetal thrombocytopenia tends to worsen in subsequent pregnancies.¹⁶⁴ In ITP the second fetus is usually as affected as the first (evidence level III).

Obstetric analgesia and anesthesia. The decision about regional anesthesia is ideally made before delivery in conjunction with the obstetric anesthetist (supplemental Document 8, Recommendation Box 11). The general trend in recent years has been to lower the "cutoff point" to 75 to $100 \times 10^9/L$.¹⁴⁵ However, there are no data to support a minimum required platelet count and each case must be individually considered, with the risk of the procedure (spinal hematoma) balanced against benefits (pain relief, better blood pressure control, avoidance of general anesthesia). There are

too few reports of epidural hematoma following regional blockade in obstetric patients to give an incidence of this complication.¹⁶⁵

In the absence of bruising, bleeding history, and anticoagulation, and if the international normalized ratio (INR), activated partial thromboplastin time (APTT) test, and fibrinogen levels are normal, a small consensus of obstetric anesthetists agree no changes to routine practice are required until the platelet count drops below $50 \times 10^9/L$. For lower counts, a careful analysis of benefit against risk of epidural hematoma is needed, and multidisciplinary discussion is encouraged. Risk of vascular damage likely decreases proportionately to needle size, and consequently spinal may be a safer option than epidural blockade. An experienced operator is required (evidence level IV).

When monitoring platelet levels, the trend, as well as the absolute value, is important, and the mother with a rapidly falling count should be observed more closely than one with low but stable levels.¹⁶⁶

Some maternity units have access to thromboelastography or other point-of-care global hemostasis monitoring.¹⁶⁷ Using this technique, thrombocytopenia can be evaluated against the prothrombotic state of pregnancy, rather than monitoring platelet function alone. However, utility of these monitors in obstetric hemostasis has never been validated¹⁶⁷ (evidence level IV).

Venous thromboembolism. Despite thrombocytopenia, ITP in pregnancy may be associated with a prothrombotic state, due to anticardiolipin antibody syndromes, or other factors more common in pregnancy, and VTE prophylaxis should be considered.

Diagnostic approach in children with suspected ITP

The diagnosis of ITP in children is one of exclusion (supplemental Document 8, Recommendation Box 12; Table 1). Children with newly diagnosed ITP and atypical features should be referred to, or discussed with, a hematologist experienced in the assessment and treatment of children with ITP. Children and their parents may benefit from contacts and literature that are available from ITP support groups (including those mentioned previously).

Differential diagnosis

Although presentation is generally acute, bruising and purpura may develop slowly over weeks or months, suggesting a chronic course. It is important to exclude other common disorders that may resemble ITP (Table 2).

If a decision is made to observe the child with presumed newly diagnosed ITP, even in typical cases, a complete blood count and blood smear should be repeated periodically to exclude the evolution of a serious bone marrow or other hematologic disorder until the diagnosis is clear or recovery has occurred.

Children with familial inherited thrombocytopenias have sometimes been misdiagnosed as having ITP.^{168,169} Inherited disorders should be suspected if thrombocytopenia has been present since early life, a positive family history for a similar disorder is elicited,¹⁷⁰ or characteristic features are present.

Special diagnostic considerations in children. Older children are more likely to have chronic disease¹⁷¹ (evidence level III). Other autoimmune diseases associated with thrombocytopenia, including SLE, CVID, and autoimmune lymphoproliferative syndrome (ALPS [although difficult to assess in some instances])

Table 7. Recommended evaluations for children newly diagnosed with ITP and no improvement after 3 to 6 months

- Bone marrow evaluation (recommended if ITP persists and no prior response)
- Tests to identify infection (HIV/HCV/H pylori) if clinical suspicion or high local prevalence
- ANA
- Testing for APLA including ACA and LAC
- Serum immunoglobulins (IgG, IgA, IgM)
- Review of medication usage

Refer also to corresponding topics under “Management of adult ITP,” and supplemental Document 6.

ANA indicates antinuclear antibody; APLA, antiphospholipid antibodies; ACA, anticardiolipin antibody; and LAC, lupus anticoagulant.

should be considered in cases with multiple autoimmune cytopenias, as should HIV infection in those with risk factors for this infection.

Bone marrow evaluation. Bone marrow evaluation in children with newly diagnosed ITP is recommended only when abnormalities are present other than isolated thrombocytopenia in the blood count/smear, if systemic features (eg, bone pain) are apparent, or if the patient has an otherwise unexplained enlarged spleen. Bone marrow evaluation should at least be considered in cases who respond minimally or not at all to first-line therapies.¹⁷²

Helicobacter pylori infection, ANA, APLA (including lupus anticoagulant [LAC]). See “*Helicobacter pylori* testing” in “Diagnostic approach in patients with suspected ITP.”

Examination of patients with persistent/early refractory ITP. For patients with an initial diagnosis of ITP and no improvement in platelet count after 3 to 6 months and who still require treatment, several evaluations are recommended (Table 7).

Management of ITP in childhood: general measures

Only 3% of children with ITP have clinically significant symptoms such as severe epistaxis or GI bleeding¹⁷³⁻¹⁷⁷ (evidence level IIb/III). Severe bleeding is more likely in children with platelet counts less than $10 \times 10^9/L$ ¹⁷⁸ (evidence level III). The incidence of ICH in children with ITP is approximately 0.1% to 0.5%^{171,179,180} (evidence level III), and predicting with confidence which children will develop an ICH is not possible. Risk factors for ICH in children with severe thrombocytopenia include head trauma and concomitant use of medications that adversely affect platelet function. Caution should be exercised in the management of children with ITP and coexisting vasculitis or coagulopathies, as may be seen in cases with varicella-associated ITP. Current opinion favors consideration of multiple factors when deciding to treat or not to treat children with ITP, including bleeding symptoms, the platelet count, and psychosocial and lifestyle issues such as activity profiles.

Table 8. Grade of severity and management of patients with ITP

Bleeding/quality of life	Management approach
Grade 1. Minor bleeding, few petechiae (≤ 100 total) and/or ≤ 5 small bruises (≤ 3 -cm diameter); no mucosal bleeding	Consent for observation
Grade 2. Mild bleeding, many petechiae (> 100 total) and/or > 5 large bruises (> 3 -cm diameter); no mucosal bleeding	Consent for observation or for treatment in selected children
Grade 3. Moderate bleeding, overt mucosal bleeding, troublesome lifestyle	Intervention to reach grade 1/2 in selected children
Grade 4. Mucosal bleeding or suspected internal hemorrhage	Intervention

Modified from Buchanan and Adix¹⁸¹; Bolton-Maggs and Moon¹⁷⁴; Imbach et al.¹⁷¹

Clinical classification

Classification of children with ITP by severity of bleeding is useful to guide management (supplemental Document 8, Recommendation Box 13; Table 8).

Three bleeding scores confirm that most children with ITP do not have serious bleeding problems despite very low platelet counts.^{173,181,182} Of note, the severity of mucocutaneous bleeding does not predict the risk for life-threatening bleeding (eg, ICH), and children should not be treated based on cutaneous signs alone without consideration of other factors including the circulating platelet count, activity profile, and psychosocial issues.

Health-related quality of life in children

Patient-reported outcomes, including health-related quality of life (HRQoL) measures, are useful components for evaluating and understanding the effects of symptoms and treatments from the patient's perspective. A disease-specific tool has now been developed—the Kid's ITP Tools (KIT)—that has reliable management properties¹⁸³ (evidence level IIa).

Expectant “watch and wait” policy

The majority of children with newly diagnosed ITP lack significant bleeding symptoms and may be managed without therapy directed at raising the platelet count at the discretion of the hematologist and the patient^{173-175,182,184-186} (evidence levels II-IV; supplemental Document 8, Recommendation Box 14). It is essential, therefore, that parents and children with ITP understand the risks of serious or life-threatening hemorrhage, and are also aware that children for whom drug therapy is prescribed are those at substantial risk of serious hemorrhage.

Hospitalization

For children with an established diagnosis of ITP, hospital admission should be reserved for those who have clinically significant bleeding. Problematic psychosocial circumstances of child and family (eg, behavioral issues, residence remote from a health care facility) should also be considered. Parents should be advised to watch for other signs of bleeding and be given a contact name and telephone number where a physician can be reached at all times. The child should not participate in competitive contact activities that have a high risk of head trauma. Other activities need not be restricted and the child should be encouraged to continue schooling (evidence level IV, grade C recommendation [supplemental Document 8, Recommendation Box 15]).

Most children with minor, mild, or moderate symptoms can be safely managed as outpatients with judicious use of supportive care (eg, antifibrinolytic agents, oral contraceptives) and weekly or less-frequent outpatient visits. When severe thrombocytopenia persists, limiting activities may be an option or treatment can be initiated. During teenage years, the issues of lifestyle and self-image assume greater importance and should also be discussed and may influence treatment decisions.

Table 9. First-line/initial treatment in children with ITP

Recommended management strategy	Approximate response rate	Approximate time to platelet recovery	Toxicities	Sustained response
IV anti-D 50-75 μ g/kg	50%-77% achieve a platelet response depending on dose	\geq 50% respond within 24 h	Headache, fever, chills (less common than with IVIg) Hemolysis, renal failure (very rare in absence of comorbidity)	Similar to IVIg although longer responses have been described with repeated dosing
IVIg single dose of 0.8-1 g/kg on d 1	Effective in more than 80% of patients	1-2 d	Side effects include headache (which can be severe), fever	Similar to corticosteroids. One-third of patients fall below acceptable platelet counts after 2-6 wk
Prednisone conventional dose 1-2 mg/kg/d for a maximum of 14 d; 4 mg/kg/d for 3-4 d	Up to three-fourths (\leq 75%) of patients will respond, depending on dose	2-7 d	Transient mood changes, gastritis, and weight gain. Caution in presence of active infection (especially varicella) or GI bleeding	No curative benefit known
Watch and wait	Approximately two-thirds of children will improve spontaneously within 6 mo	Days to ~ 6 mo	Preventable hemorrhage occurs, activity restriction, anxiety	Spontaneous remissions are generally durable

TPO-receptor agonists: studies in children are ongoing. At this time, evidence to support use of these agents in children is not available, but encouraging results have been reported in adults (see "Management of adult ITP").

More complete details regarding the studies found in the literature search (2001-2008) are available in supplemental Document 7.

General measures for persistent and chronic ITP in children

The management of children with persistent/refractory ITP is essentially the same as those with newly diagnosed ITP. Many children stabilize with an adequate platelet count ($> 20-30 \times 10^9/L$) and have no symptoms unless injured. Spontaneous remission may occur over time and expectant management can continue depending on the risk of bleeding and the degree of activity restriction of the child. The onset of menstruation may be problematic and can be managed with antifibrinolytic agents and hormonal medication (see "Supportive care" under "Management of adult ITP"). Children and parents should not forget the vulnerability to excessive bleeding following serious accidents and it is advisable for the family to carry a card or letter with details of the disorder in case of emergency. A medical bracelet or pendant may be appropriate (evidence level IV).

Some children with ITP will have platelet counts of 10 to $30 \times 10^9/L$ and, although they have no serious bleeding, they are nonetheless troubled by purpura. Treatment may be beneficial in these cases. As adolescents, minors may become very conscious of their appearance and need sympathetic support.

Management of ITP in children

It is necessary to treat all children with severe bleeding symptoms and treatment should also be considered in children with moderate bleeding or those at increased risk of bleeding (Table 9).

First-line/initial treatment options to raise platelet counts in children

See supplemental Document 8, Recommendation Box 16.

Intravenous anti-D immunoglobulin. IV anti-D immunoglobulin can be given to Rh(D)-positive children as a short infusion and

is usually effective in transiently raising platelet counts.^{47,48,52,187,188} Mild extravascular hemolysis is common and a few instances of intravascular hemolysis, disseminated intravascular coagulation, and renal failure have been reported in pediatric patients with comorbidities.^{44,53,189,190}

Intravenous immunoglobulin (IVIg). IVIg raises the platelet count in more than 80% of children and does so more rapidly than corticosteroids or no therapy¹⁹¹⁻¹⁹⁴ (evidence level Ia/Ib). Transient side effects (fever, headache, nausea/vomiting) are highest with a dose of 1 g/kg given on consecutive days¹⁹⁵ (evidence level Ia-III).

The original IVIg dose of 0.4 g/kg daily for 2 to 5 days has been superseded by short course with a single dose of 0.8 to 1 g/kg, with possible repeat treatment based on the short-term platelet response^{47,196} (evidence level Ib).

Prednisone/corticosteroids. Prednisone at a dose of 1 to 2 mg/kg/d may be effective at inducing a response in children^{15,16} (evidence level Ib). Higher doses (4 mg/kg/d) for 3 to 4 days have been shown to be effective in up to 72% to 88% of children (platelet count $> 50 \times 10^9/L$) within 72 hours^{187,195,197} (evidence level Ib/III).

Because of the serious side effects associated with prolonged corticosteroid treatment in children with ITP, prednisone should be used only to maintain a hemostatic platelet count, and for as short a time as possible.

Emergency treatment in children

In organ- or life-threatening situations (as with adult patients), a larger-than-usual dose (2- to 3-fold) of platelets should be infused together with IV high-dose corticosteroids and IVIg or IV anti-D (supplemental Document 8, Recommendation Box 17). The goal of treatment is to elevate the platelet count to a level where the risk of

Table 10. Treatment options in children with persistent or chronic ITP

Recommended treatment strategy	Approximate response rate	Approximate time to response	Toxicities	Sustained response
Dexamethasone 28 mg/m ² /d	Up to 80% achieve a platelet response (study in adults and children)	3 d	Sleeplessness, behavioral changes, hypertension, anxiety, gastric distress, cataract, bronchial pneumonia, fatigue, pain	Responses are of short duration unless cycles are repeated
HDMP 30 mg/kg/d for 3 d followed by 20 mg/kg/d for 4 d	At least as effective as IVIg; 60%-100% of patients achieve platelet response	2-7 d	Worse side-effect profile compared with prednisone	
Rituximab 100 mg or 375 mg/m ² /wk for 4 wk	31%-79% response rates reported (CR/PR/MR)	Within a few weeks	Generally well tolerated. Side effects mild and easily resolved: serum sickness, maculopapular rash, arthralgia, low-grade fever, malaise, pruritus, urticaria, and throat tightness	63% achieved a CR lasting 4 to 30 mo; however, this is variable in literature
Single or combination regimens: cyclosporin A, azathioprine, prednisone, IVIg, anti-D, vinca alkaloids, and danazol	Approximately 70% of patients achieve platelet response	Days to months	Cytotoxic agents: usual side effects of monotherapies apply, consideration of carcinogenesis required	Individual responses vary
Splenectomy	60%-70% long-term response	24 h	Postsplenectomy complications include sepsis	80% of responders maintain platelet response over 4 y

See supplemental Document 7 for relevant studies. More complete details regarding the studies found in the literature search (2001-2008) are available in the appendices.

HDMP indicates high-dose methylprednisolone; CR, complete response; PR, partial response; and MR, minor response.

severe bleeding is minimized as soon as possible. In special circumstances, emergency splenectomy may need to be considered (evidence level IV).

Treatment options for children with persistent or chronic ITP

The goal of treatment for children with persistent or chronic ITP is to maintain a hemostatic platelet count with first-line therapies (eg, IVIg, IV anti-D, short-course corticosteroids) and to minimize the use of prolonged corticosteroid therapy (supplemental Document 8, Recommendation Box 18). Cytotoxic drugs should be used with extreme caution in children. All children with persistent or chronic ITP should have their case reviewed and managed by a hematologist experienced in the diagnosis and management of children with ITP.

Table 10 contains a summary of the treatment options for children with chronic ITP in whom first-line treatments are not successful. Treatment options are listed alphabetically and do not imply preference.

Dexamethasone. Dexamethasone (28-40 mg/m²/d) has been reported as treatment for patients with refractory ITP.^{198,199} The response rate in previously untreated patients aged 18 years or younger was 86%, with 67% of all evaluable patients reaching platelet levels of at least $50 \times 10^9/L$ lasting for a median time of 26 months³⁶ (evidence level IIa). However, side effects such as sleeplessness, aggressive behavior, and loss of concentration are unacceptably high.¹⁹⁸

High-dose methylprednisolone. HDMP (given as an oral 7-day course of 30 mg/kg/d for 3 days followed by 20 mg/kg/d for

4 days) has been used as an alternative to IVIg²⁰⁰⁻²⁰² (evidence level Ib-III).

IVIg/anti-D. See "First-line/initial treatment options to raise platelet counts in children."

Rituximab (see "Rituximab" in "Second-line treatment options for adult ITP patients"). Rituximab has been used with success in children with chronic refractory ITP²⁰³⁻²⁰⁵ (evidence levels IIa and IIb). Overall, the response rate ($> 50 \times 10^9/L$ platelet count) is between 31% and 68%. In all case series, rituximab was well tolerated with the exception of serum sickness (supplemental Document 7).

Single or combination regimens (see "Combination chemotherapy" in "Treatment options for adult patients failing first- and second-line therapies"). The experience in children is limited and therefore no recommendations can be made⁶⁵ (evidence level IIb/IV).

TPO-receptor agonists. A number of studies with TPO-receptor agonists have shown encouraging results in adults.^{90,92-98} However, no finalized studies in children are available to support the use of these agents in this patient population. Assuming that the long-term safety of these agents is confirmed, they could be used not only for children with chronic refractory ITP, but also in those with persistent but highly symptomatic disease resistant to usual first-line treatments.

Surgical options for children with chronic refractory ITP

Bleeding complications of ITP must be managed according to severity and circumstances, and splenectomy is generally deferred

for as long as possible. Seventy to 80% of children will initially respond to splenectomy but the postoperative risk of infection is a deterrent to its routine use.

Splenectomy. Splenectomy with appropriate previous vaccination, followed by prophylactic antibiotics, is an effective treatment for pediatric ITP (supplemental Document 8, Recommendation Box 19). However, it is rarely recommended in children because the risk of death from ITP in childhood is extremely low (< 0.5%). The comparative figure associated with postsplenectomy overwhelming sepsis is up to 3% in children.²⁰⁶ The risk of sepsis probably persists for life. In children who do undergo splenectomy, the overall effectiveness is good, but complications, primarily sepsis, remain a concern^{206,207} (evidence level IIb/III).

Therapies whose use is no longer justified

Consensus regarding a lack of efficacy or high reported toxicity, or because of a lack of evidence means that interferon- α and campath-1H can no longer be justified for use in childhood ITP (evidence level IV).

Conclusions

Despite significant progress in our understanding of the pathophysiology and management of ITP during the past 15 years, surprisingly few RCTs have been conducted and evidence-based guidelines to inform management of individual patients are limited. There are also few validated risk factors regarding outcome prediction or response to therapies (including splenectomy) and little progress has been made toward making ITP anything other than a "diagnosis of exclusion." Consequently, future research on ITP must be focused on carefully designed randomized trials and multicenter prospective cohort studies.

Addendum

Anti-D immunoglobulin may not be available in all countries, and in June 2009, the European Medicines Agency was formally notified by Cangene Europe Ltd of its decision to withdraw all its applications and all marketing authorizations for their anti-D immunoglobulin product WinRho SDF.

Acknowledgments

The writing and project management of this consensus document were supported by an unrestricted grant provided by Amgen Ltd, Baxter Ltd, and GlaxoSmithKline Ltd. Frances Essex, MSc, Senior Medical Writer, ScopeMedical Ltd, provided writing assistance throughout the project; Rebecca Hunt, Account Director, ScopeMedical Ltd, provided project management; and Keely Jennings BA, Editorial Services Manager, ScopeMedical Ltd, provided editorial assistance throughout the project.

Authorship

Contribution: D.P., A.C.N., D.J.K., R.S., D.B.C., P.A.I., V.S.B., B.J.H., and T.B.G. wrote the paper; D.P., D.J.K., R.S., and V.S.B.

analyzed data; A.C.N. led the manuscript review; D.J.K. led manuscript review for adult ITP; R.S. and D.B.C. led manuscript review for the diagnosis of ITP; P.A.I. and V.S.B. led manuscript review for pediatric ITP; B.J.H. and T.B.G. led manuscript review for ITP in pregnancy; and J.G., P.B.-M., M.T., I.G., G.L., R.M., J.B.B., F.R., B.H.C., B.G., M.A.S., S.W., and J.Y. reviewed the manuscript.

Conflict-of-interest disclosure: D.P. serves as a consultant for Amgen, GlaxoSmithKline (GSK), Shionogi, ONO, and Eisai; receives research support from Amgen, GSK, and Baxter Healthcare; and serves on the speakers bureau for Amgen. R.S. receives honoraria for participation on advisory boards and/or as a speaker at medical education events supported by GSK and Amgen. A.C.N. receives research funding from Amgen, Baxter, GSK, and Genentech; serves on speaking panels for Amgen and GSK and on advisory boards for GSK and PanGenetics; has no financial interest (stocks and shares); is not employed by any relevant company; and has no patents pending. V.S.B. serves on the Bayer International Haemophilia Advisory Board and is a member and chair of Novo Nordisk PRO-PACT Advisory Board. P.B.M. receives support from Baxter for travel to international meetings (International Society on Thrombosis and Haemostasis Scientific and Standardization Committee meeting, Vienna, Austria, 2008, and American Society of Hematology meeting, New Orleans, LA, 2009); participates in advisory board meetings for both Amgen and GSK; and served as chair of a satellite meeting for Baxter at the 2009 British Society for Haematology meeting. J.B.B. receives clinical research support from Amgen, Biogen-IDEc, Cangene, Genentech, GSK, Genzyme, Immunomedics, Ligand, MGI Pharma/Eisai Inc, and Sysmex; participates in speakers bureau programs for Baxter, Amgen, and GSK; owns stock in Amgen and GSK; participates in advisory boards for Amgen, GSK, Ligand, and Baxter; and participates in discussions of unlabeled or investigational use of product(s) that might include anti-cd40 ligand, thrombopoietic agents (AMG531 [Amgen], Eltrombopag [GSK], AKR501 [AkaRx]), Rigel, and rituximab [Genentech/Biogen-IDEc]. B.H.C. is a member of the scientific advisory boards of GSK, Amgen, Commonwealth Serum Laboratory (CSL), Bayer, and Boehringer Ingelheim; and serves as a consultant for CSL and Boehringer Ingelheim. D.B.C. serves as a consultant for Amgen, GSK, Symphogen, Genzyme, and Shionogi. T.B.G. receives research funding from and serves as a consultant for Amgen and GSK. B.G. serves as a consultant for Roche France, Amgen, and Laboratoire de fractionnement et de Biotechnologies (LFB; Les Ulis, France). J.G. receives honoraria for participation on advisory boards for GSK, Amgen, and Baxter, and receives research support from Baxter. B.J.H. lectures at meetings sponsored by Baxter. P.A.I. receives research funding from Amgen, GSK, and Roche, and serves as a consultant for Symphogen. R.M. owns stock in GSK and serves as ad hoc consultant for Amgen and GSK. F.R. receives honoraria for participation in advisory boards and/or as a speaker at medical education events supported by Amgen, GSK, and Shionogi. D.J.K. receives research support from and serves as a consultant for GSK, Amgen, MGI Pharma, Ligand, ONO, and Shionogi. I.G., G.L., M.A.S., M.T., S.W., and J.Y. declare no competing financial interests.

Correspondence: Drew Provan, Barts and The London School of Medicine and Dentistry, Dept of Haematology, 80 Newark St, London, E1 2ES, United Kingdom; e-mail: a.b.provan@qmul.ac.uk.

References

- Rodeghiero F, Stasi R, Gernsheimer T, et al. Standardization of terminology, definitions and outcome criteria in immune thrombocytopenic purpura of adults and children: report from an international working group. *Blood*. 2009;113(11):2386-2393.
- Olsson B, Andersson PO, Jernas M, et al. T-cell-mediated cytotoxicity toward platelets in chronic idiopathic thrombocytopenic purpura. *Nat Med*. 2003;9(9):1123-1124.
- Chang M, Nakagawa PA, Williams SA, et al. Immune thrombocytopenic purpura (ITP) plasma and purified ITP monoclonal autoantibodies inhibit megakaryocytopoiesis in vitro. *Blood*. 2003;102(3):887-895.
- McMillan R, Wang L, Tomer A, Nichol J, Pistillo J. Suppression of in vitro megakaryocyte production by antiplatelet autoantibodies from adult patients with chronic ITP. *Blood*. 2004;103(4):1364-1369.
- Houwerzijl EJ, Blom NR, van der Want JJ, et al. Ultrastructural study shows morphologic features of apoptosis and para-apoptosis in megakaryocytes from patients with idiopathic thrombocytopenic purpura. *Blood*. 2004;103(2):500-506.
- Zhang F, Chu X, Wang L, et al. Cell-mediated lysis of autologous platelets in chronic idiopathic thrombocytopenic purpura. *Eur J Haematol*. 2006;76(5):427-431.
- Neylon AJ, Saunders PW, Howard MR, Proctor SJ, Taylor PR. Clinically significant newly presenting autoimmune thrombocytopenic purpura in adults: a prospective study of a population-based cohort of 245 patients. *Br J Haematol*. 2003;122(6):966-974.
- Segal JB, Powe NR. Prevalence of immune thrombocytopenia: analyses of administrative data. *J Thromb Haemost*. 2006;4(11):2377-2383.
- Stasi R, Stipa E, Masi M, et al. Long-term observation of 208 adults with chronic idiopathic thrombocytopenic purpura. *Am J Med*. 1995;98(5):436-442.
- Kühne T, Imbach P, Bolton-Maggs PH, et al. Newly diagnosed idiopathic thrombocytopenic purpura in childhood: an observational study. *Lancet*. 2001;358(9299):2122-2125.
- Stasi R, Evangelista ML, Stipa E, et al. Idiopathic thrombocytopenic purpura: current concepts in pathophysiology and management. *Thromb Haemost*. 2008;99(1):4-13.
- Kühne T, Buchanan GR, Zimmerman S, et al. A prospective comparative study of 2540 infants and children with newly diagnosed idiopathic thrombocytopenic purpura (ITP) from the International Childhood ITP Study Group. *J Pediatr*. 2003;143(5):605-608.
- Miller E, Waight P, Farrington CP, et al. Idiopathic thrombocytopenic purpura and MMR vaccine. *Arch Dis Child*. 2001;84(3):227-229.
- Braester A. Pseudothrombocytopenia as a pitfall in the treatment of essential thrombocythemia. *Eur J Haematol*. 2003;70(4):251-252.
- George JN, Woolf SH, Raskob GE, et al. Idiopathic thrombocytopenic purpura: a practice guideline developed by explicit methods for the American Society of Hematology. *Blood*. 1996;88(1):3-40.
- Guidelines for the investigation and management of idiopathic thrombocytopenic purpura in adults, children and in pregnancy. *Br J Haematol*. 2003;120(4):574-596.
- Mak YK, Yu PH, Chan CH, Chu YC. The management of isolated thrombocytopenia in Chinese adults: does bone marrow examination have a role at presentation? *Clin Lab Haematol*. 2000;22(6):355-358.
- Jubelirer SJ, Harpold R. The role of the bone marrow examination in the diagnosis of immune thrombocytopenic purpura: case series and literature review. *Clin Appl Thromb Hemost*. 2002;8(1):73-76.
- Mittal S, Blaylock MG, Culligan DJ, Barker RN, Vickers MA. A high rate of CLL phenotype lymphocytes in autoimmune hemolytic anemia and immune thrombocytopenic purpura. *Haematologica*. 2008;93(1):151-152.
- Stasi R, Sarpatwari A, Segal JB. Effects of eradication of *Helicobacter pylori* infection in patients with immune thrombocytopenic purpura. A systematic review. *Blood*. 2009;113(6):1231-1240.
- Liebman HA, Stasi R. Secondary immune thrombocytopenic purpura. *Curr Opin Hematol*. 2007;14(5):557-573.
- Aledort LM, Hayward CP, Chen MG, Nichol JL, Bussell J. Prospective screening of 205 patients with ITP, including diagnosis, serological markers, and the relationship between platelet counts, endogenous thrombopoietin, and circulating anti-thrombopoietin antibodies. *Am J Hematol*. 2004;76(3):205-213.
- Brighton TA, Evans S, Castaldi PA, Chesterman CN, Chong BH. Prospective evaluation of the clinical usefulness of an antigen-specific assay (MAIPA) in idiopathic thrombocytopenic purpura and other immune thrombocytopenias. *Blood*. 1996;88(1):194-201.
- McMillan R, Wang L, Tani P. Prospective evaluation of the immunobead assay for the diagnosis of adult chronic immune thrombocytopenic purpura (ITP). *J Thromb Haemost*. 2003;1(3):485-491.
- Stasi R, Stipa E, Masi M, et al. Prevalence and clinical significance of elevated antiphospholipid antibodies in patients with idiopathic thrombocytopenic purpura. *Blood*. 1994;84(12):4203-4208.
- Altintas A, Ozel A, Okur N, et al. Prevalence and clinical significance of elevated antinuclear antibody test in children and adult patients with idiopathic thrombocytopenic purpura. *J Thromb Thrombolysis*. 2007;24(2):163-168.
- Liebman H. Other immune thrombocytopenias. *Semin Hematol*. 2007;44(4 suppl 5):S24-S34.
- Cohen YC, Djulbegovic B, Shamai-Lubovitz O, Mozes B. The bleeding risk and natural history of idiopathic thrombocytopenic purpura in patients with persistent low platelet counts. *Arch Intern Med*. 2000;160(11):1630-1638.
- Cortelazzo S, Finazzi G, Buelli M, et al. High risk of severe bleeding in aged patients with chronic idiopathic thrombocytopenic purpura. *Blood*. 1991;77(1):31-33.
- Portielje JE, Westendorp RG, Kluin-Nelemans HC, Brand A. Morbidity and mortality in adults with idiopathic thrombocytopenic purpura. *Blood*. 2001;97(9):2549-2554.
- Yang R, Han ZC. Pathogenesis and management of chronic idiopathic thrombocytopenic purpura: an update. *Int J Hematol*. 2000;71(1):18-24.
- Kitchens CS, Weiss L. Ultrastructural changes of endothelium associated with thrombocytopenia. *Blood*. 1975;46(4):567-578.
- Kitchens CS. Amelioration of endothelial abnormalities by prednisone in experimental thrombocytopenia in the rabbit. *J Clin Invest*. 1977;60(5):1129-1134.
- McMillan R. Chronic idiopathic thrombocytopenic purpura. *N Engl J Med*. 1981;304(19):1135-1147.
- Bussell JB. Autoimmune thrombocytopenic purpura. *Hematol Oncol Clin North Am*. 1990;4(1):179-191.
- Ben-Yehuda D, Gillis S, Eldor A. Clinical and therapeutic experience in 712 Israeli patients with idiopathic thrombocytopenic purpura. Israeli ITP Study Group. *Acta Haematol*. 1994;91(1):1-6.
- George JN, el-Harake MA, Raskob GE. Chronic idiopathic thrombocytopenic purpura. *N Engl J Med*. 1994;331(18):1207-1211.
- Pizzuto J, Ambriz R. Therapeutic experience on 934 adults with idiopathic thrombocytopenic purpura: Multicentric Trial of the Cooperative Latin American group on Hemostasis and Thrombosis. *Blood*. 1984;64(6):1179-1183.
- Andersen JC. Response of resistant idiopathic thrombocytopenic purpura to pulsed high-dose dexamethasone therapy. *N Engl J Med*. 1994;330(22):1560-1564.
- Stasi R, Brunetti M, Pagano A, et al. Pulsed intravenous high-dose dexamethasone in adults with chronic idiopathic thrombocytopenic purpura. *Blood Cells Mol Dis*. 2000;26(6):582-586.
- Mazzucconi MG, Fazi P, Bernasconi S, et al. Therapy with high-dose dexamethasone (HD-DXM) in previously untreated patients affected by idiopathic thrombocytopenic purpura: a GIMEMA experience. *Blood*. 2007;109(4):1401-1407.
- von dem Borne AE, Vos JJ, Pegels JG, Thomas LL, van dL. High dose intravenous methylprednisolone or high dose intravenous gammaglobulin for autoimmune thrombocytopenia. *Br Med J (Clin Res Ed)*. 1988;296(6617):249-250.
- Alpdogan O, Budak-Alpdogan T, Ratip S, et al. Efficacy of high-dose methylprednisolone as a first-line therapy in adult patients with idiopathic thrombocytopenic purpura. *Br J Haematol*. 1998;103(4):1061-1063.
- Gaines AR. Disseminated intravascular coagulation associated with acute hemoglobinemia or hemoglobinuria following Rh(0)(D) immune globulin intravenous administration for immune thrombocytopenic purpura. *Blood*. 2005;106(5):1532-1537.
- Gaines AR. Acute onset hemoglobinemia and/or hemoglobinuria and sequelae following Rh (o) (D) immune globulin intravenous administration in immune thrombocytopenic purpura patients. *Blood*. 2000;95(8):2523-2529.
- Cardo LJ, Strack M, Williams J. Anti-D for the treatment of splenectomized patients with immune thrombocytopenic purpura. *Blood*. 1991;78(10):2786-2787.
- Tarantino MD, Madden RM, Fennwald DL, Patel CC, Bertolone SJ. Treatment of childhood acute immune thrombocytopenic purpura with anti-D immune globulin or pooled immune globulin. *J Pediatr*. 1999;134(1):21-26.
- Scaradavou A, Woo B, Woloski BM, et al. Intravenous anti-D treatment of immune thrombocytopenic purpura: experience in 272 patients. *Blood*. 1997;89(8):2689-2700.
- Cooper N, Woloski BM, Fodero EM, et al. Does treatment with intermittent infusions of intravenous anti-D allow a proportion of adults with recently diagnosed immune thrombocytopenic purpura to avoid splenectomy? *Blood*. 2002;99(6):1922-1927.
- George JN, Raskob GE, Vesely SK, et al. Initial management of immune thrombocytopenic purpura in adults: a randomized controlled trial comparing intermittent anti-D with routine care. *Am J Hematol*. 2003;74(3):161-169.
- Newman GC, Novoa MV, Fodero EM, et al. A dose of 75 microg/kg/d of i.v. anti-D increases the platelet count more rapidly and for a longer period of time than 50 microg/kg/d in adults with immune thrombocytopenic purpura. *Br J Haematol*. 2001;112(4):1076-1078.
- Tarantino MD, Young G, Bertolone SJ, et al. Single dose of anti-D immune globulin at 75 microg/kg is as effective as intravenous immune globulin at rapidly raising the platelet count in newly diagnosed immune thrombocytopenic purpura in children. *J Pediatr*. 2006;148(4):489-494.
- Tarantino MD, Bussell JB, Cines DB, et al. A closer look at intravascular hemolysis (IVH) following intravenous anti-D for immune thrombocytopenic purpura (ITP). *Blood*. 2007;109(12):5527.

54. Gringeri A, Cattaneo M, Santagostino E, Mannucci PM. Intramuscular anti-D immunoglobulins for home treatment of chronic immune thrombocytopenic purpura. *Br J Haematol*. 1992; 80(3):337-40.
55. Borgna-Pignatti C, Battisti L, Zecca M, Locatelli F. Treatment of chronic childhood immune thrombocytopenic purpura with intramuscular anti-D immunoglobulins. *Br J Haematol*. 1994;88(3):618-620.
56. Meyer O, Kiesewetter H, Hermesen M, et al. Replacement of intravenous administration of anti-D by subcutaneous administration in patients with autoimmune thrombocytopenia. *Pediatr Blood*. 2006;47(5 suppl):721-722.
57. Kjaersgaard M, Edslev PW, Hasle H. Subcutaneous anti-D treatment of idiopathic thrombocytopenic purpura in children. *Pediatr Blood Cancer*. 2009;53(7):1315-1317.
58. Newland AC, Treleaven JG, Minchinton RM, Waters AH. High-dose intravenous IgG in adults with autoimmune thrombocytopenia. *Lancet*. 1983;1(8316):84-87.
59. Cunningham-Rundles C, Knight AK. Common variable immune deficiency: reviews, continued puzzles, and a new registry. *Immunol Res*. 2007; 38(1-3):78-86.
60. Bussell J. Intravenous immune serum globulin in immune thrombocytopenia: clinical results and biochemical evaluation. *Vox Sang*. 1985;49(suppl 1):44-50.
61. Schiavotto C, Ruggeri M, Rodeghiero F. Adverse reactions after high-dose intravenous immunoglobulin: incidence in 83 patients treated for idiopathic thrombocytopenic purpura (ITP) and review of the literature. *Haematologica*. 1993;78(6 suppl 2):35-40.
62. Cayco AV, Perazella MA, Hayslett JP. Renal insufficiency after intravenous immune globulin therapy: a report of two cases and an analysis of the literature. *J Am Soc Nephrol*. 1997;8(11): 1788-1794.
63. Spahr JE, Rodgers GM. Treatment of immune-mediated thrombocytopenia purpura with concurrent intravenous immunoglobulin and platelet transfusion: a retrospective review of 40 patients. *Am J Hematol*. 2008;83(2):122-125.
64. Carr JM, Kruskall MS, Kaye JA, Robinson SH. Efficacy of platelet transfusions in immune thrombocytopenia. *Am J Med*. 1986;80(6):1051-1054.
65. Boruchov DM, Gururangan S, Driscoll MC, Bussell JB. Multiagent induction and maintenance therapy for patients with refractory immune thrombocytopenic purpura (ITP). *Blood*. 2007; 110(10):3526-3531.
66. Masseau A, Guittion C, Bretonniere C, et al. [Plasma exchanges as treatment of severe acute immune thrombocytopenic purpura]. *Rev Med Interne*. 2005;26(10):824-826.
67. Quiquandon I, Fenaux P, Caulier MT, et al. Re-evaluation of the role of azathioprine in the treatment of adult chronic idiopathic thrombocytopenic purpura: a report on 53 cases. *Br J Haematol*. 1990;74(2):223-228.
68. Yenson PR, Forrest D, Schmiegelow K, Dalal BI. Azathioprine-associated acute myeloid leukemia in a patient with Crohn's disease and thiopurine S-methyltransferase deficiency. *Am J Hematol*. 2008;83(1):80-83.
69. Emilia G, Morselli M, Luppi M, et al. Long-term salvage therapy with cyclosporin A in refractory idiopathic thrombocytopenic purpura. *Blood*. 2002;99(4):1482-1485.
70. Kappers-Klunne MC, van't Veer MB. Cyclosporin A for the treatment of patients with chronic idiopathic thrombocytopenic purpura refractory to corticosteroids or splenectomy. *Br J Haematol*. 2001;114(1):121-125.
71. Verlin M, Laros RK Jr, Penner JA. Treatment of refractory thrombocytopenic purpura with cyclophosphamide. *Am J Hematol*. 1976;1(1):97-104.
72. Reiner A, Gernsheimer T, Slichter SJ. Pulse cyclophosphamide therapy for refractory autoimmune thrombocytopenic purpura. *Blood*. 1995; 85(2):351-358.
73. Krause JR. Chronic idiopathic thrombocytopenic purpura (ITP): development of acute non-lymphocytic leukemia subsequent to treatment with cyclophosphamide. *Med Pediatr Oncol*. 1982;10(1):61-65.
74. Maloel F, Andres E, Zimmer J, et al. Danazol therapy in patients with chronic idiopathic thrombocytopenic purpura: long-term results. *Am J Med*. 2004;116(9):590-594.
75. Vancine-Califani SM, De Paula EV, Ozelo MC, et al. Efficacy and safety of dapsone as a second-line treatment in non-splenectomized adults with immune thrombocytopenic purpura. *Platelets*. 2008;19(7):489-495.
76. Hernández F, Linares M, Colomina P, et al. Dapsone for refractory chronic idiopathic thrombocytopenic purpura. *Br J Haematol*. 1995;90(2):473-475.
77. Fanello CI, Karema C, Avellino P, et al. High risk of severe anaemia after chlorproguanil-dapsone+ artesunate antimalarial treatment in patients with G6PD (A-) deficiency. *PLoS ONE*. 2008;3(12): e4031.
78. Provan D, Moss AJ, Newland AC, Bussell JB. Efficacy of mycophenolate mofetil as single-agent therapy for refractory immune thrombocytopenic purpura. *Am J Hematol*. 2006;81(1):19-25.
79. Kotb R, Pinganaud C, Trichet C, et al. Efficacy of mycophenolate mofetil in adult refractory autoimmune cytopenias: a single center preliminary study. *Eur J Haematol*. 2005;75(1):60-64.
80. Arnold DM, Dentali F, Crowther MA, et al. Systematic review: efficacy and safety of rituximab for adults with idiopathic thrombocytopenic purpura. *Ann Intern Med*. 2007;146(1):25-33.
81. Stasi R, Stipa E, Forte V, Meo P, Amadori S. Variable patterns of response to rituximab treatment in adults with chronic idiopathic thrombocytopenic purpura. *Blood*. 2002;99(10):3872-3873.
82. Cooper N, Stasi R, Cunningham-Rundles S, et al. The efficacy and safety of B-cell depletion with anti-CD20 monoclonal antibody in adults with chronic immune thrombocytopenic purpura. *Br J Haematol*. 2004;125(2):232-239.
83. Godeau B, Porcher R, Fain O, et al. Rituximab efficacy and safety in adult splenectomy candidates with chronic immune thrombocytopenic purpura: results of a prospective multicenter phase 2 study. *Blood*. 2008;112(4):999-1004.
84. Provan D, Butler T, Evangelista ML, et al. Activity and safety profile of low-dose rituximab for the treatment of autoimmune cytopenias in adults. *Haematologica*. 2007;92(12):1695-1698.
85. Zaja F, Battista ML, Pirodda MT, et al. Lower dose rituximab is active in adults patients with idiopathic thrombocytopenic purpura. *Haematologica*. 2008;93(6):930-933.
86. Fianchi L, Rossi E, Murri R, et al. Severe infectious complications in a patient treated with rituximab for idiopathic thrombocytopenic purpura. *Ann Hematol*. 2007;86(3):225-226.
87. Carson KR, Evens AM, Richey EA, et al. Progressive multifocal leukoencephalopathy after rituximab therapy in HIV-negative patients: a report of 57 cases from the Research on Adverse Drug Events and Reports project. *Blood*. 2009;113(20): 4834-4840.
88. Federal Drug Administration. FDA warning. <http://www.fda.gov/Drugs/DrugSafety/DrugSafetyNewsletter/ucm115974.htm#RituximabmarketedasRituxan>: ProgressiveMultifocalLeukoencephalopathyPML. Accessed December 14, 2009.
89. Kaushansky K. Thrombopoietin: the primary regulator of megakaryocyte and platelet production. *Thromb Haemost*. 1995;74(1):521-525.
90. Bussell JB, Kuter DJ, George JN, et al. AMG 531, a thrombopoiesis-stimulating protein, for chronic ITP. *N Engl J Med*. 2006;355(16):1672-1681.
91. Kuter DJ. New thrombopoietic growth factors. *Blood*. 2007;109(11):4607-4616.
92. Bussell JB, Cheng G, Saleh MN, et al. Eltrombopag for the treatment of chronic idiopathic thrombocytopenic purpura. *N Engl J Med*. 2007;357(22): 2237-2247.
93. Kuter DJ, Bussell JB, Lyons RM, et al. Efficacy of romiplostim in patients with chronic immune thrombocytopenic purpura: a double-blind randomised controlled trial. *Lancet*. 2008;371(9610): 395-403.
94. Bussell JB, Provan D, Shamsi T, et al. Effect of eltrombopag on platelet counts and bleeding during treatment of chronic idiopathic thrombocytopenic purpura: a randomised, double-blind, placebo-controlled trial. *Lancet*. 2009;373(9664): 641-648.
95. Jenkins JM, Williams D, Deng Y, et al. Phase 1 clinical study of eltrombopag, an oral, nonpeptide thrombopoietin receptor agonist. *Blood*. 2007; 109(11):4739-4741.
96. Kumagai Y, Fujita T, Ozaki M, et al. Pharmacodynamics and pharmacokinetics of AMG 531, a thrombopoiesis-stimulating peptibody, in healthy Japanese subjects: a randomized, placebo-controlled study. *J Clin Pharmacol*. 2007;47(12): 1489-1497.
97. Newland A, Caulier MT, Kappers-Klunne M, et al. An open-label, unit dose-finding study of AMG 531, a novel thrombopoiesis-stimulating peptibody, in patients with immune thrombocytopenic purpura. *Br J Haematol*. 2006;135(4):547-553.
98. Bussell JB, Kuter DJ, Pullarkat V, et al. Safety and efficacy of long-term treatment with romiplostim in thrombocytopenic patients with chronic ITP. *Blood*. 2009;113(10):2161-2171.
99. GlaxoSmithKline Ltd. Promacta (Eltrombopag tablet) FDA oncologic drug advisory committee briefing document. <http://www.fda.gov/ohrms/dockets/AC/08/briefing/2008-4366b1-02-GSK.pdf>. Accessed September 23, 2009.
100. Cheng G. Oral Eltrombopag for the long-term treatment of patients with chronic idiopathic thrombocytopenic purpura: results of a phase III, double-blind, placebo-controlled study (RAISE) [abstract]. *Blood*. 2008;112(11):Abstract 400.
101. Berchtold P, McMillan R. Therapy of chronic idiopathic thrombocytopenic purpura in adults. *Blood*. 1989;74(7):2309-2317.
102. Szczepanik AB, Sikorska A, Slomkowski M, Konopka L. The use of vinca alkaloids in preparation for splenectomy of corticosteroid refractory chronic immune thrombocytopenic purpura patients. *Int J Lab Hematol*. 2007;29(5):347-351.
103. Schwartz J, Leber MD, Gillis S, et al. Long term follow-up after splenectomy performed for immune thrombocytopenic purpura (ITP). *Am J Hematol*. 2003;72(2):94-98.
104. Kojouri K, Vesely SK, Terrell DR, George JN. Splenectomy for adult patients with idiopathic thrombocytopenic purpura: a systematic review to assess long-term platelet count responses, prediction of response, and surgical complications. *Blood*. 2004;104(9):2623-2634.
105. Vianelli N, Galli M, de Vivo A, et al. Efficacy and safety of splenectomy in immune thrombocytopenic purpura: long-term results of 402 cases. *Haematologica*. 2005;90(1):72-77.
106. Johansson E, Engervall P, Landgren O, et al. Response to splenectomy is durable after a certain point in time in adult patients with chronic immune thrombocytopenic purpura. *Eur J Haematol*. 2006;77(1):61-66.
107. Keidar A, Sagi B, Szold A. Laparoscopic splenectomy for immune thrombocytopenic purpura in patients with severe refractory thrombocytopenia. *Pathophysiol Haemost Thromb*. 2003;33(2):116-119.
108. Naouri A, Feghali B, Chabal J, et al. Results of

- splenectomy for idiopathic thrombocytopenic purpura. Review of 72 cases. *Acta Haematol.* 1993; 89(4):200-203.
109. McMillan R, Durette C. Long-term outcomes in adults with chronic ITP after splenectomy failure. *Blood.* 2004;104(4):956-960.
 110. Law C, Marcaccio M, Tam P, Heddle N, Kelton JG. High-dose intravenous immune globulin and the response to splenectomy in patients with idiopathic thrombocytopenic purpura. *N Engl J Med.* 1997;336(21):1494-1498.
 111. Bussel JB, Kaufmann CP, Ware RE, Woloski BM. Do the acute platelet responses of patients with immune thrombocytopenic purpura (ITP) to IV anti-D and to IV gammaglobulin predict response to subsequent splenectomy? *Am J Hematol.* 2001;67(1):27-33.
 112. Najean Y, Rain JD, Billotey C. The site of destruction of autologous 111In-labelled platelets and the efficiency of splenectomy in children and adults with idiopathic thrombocytopenic purpura: a study of 578 patients with 268 splenectomies. *Br J Haematol.* 1997;97(3):547-550.
 113. Rossi G, Cattaneo C, Motta M, et al. Platelet kinetic study in patients with idiopathic thrombocytopenic purpura (ITP) refractory or relapsing after corticosteroid treatment. *Hematol J.* 2002;3(3):148-152.
 114. Facon T, Caulier MT, Fenaux P, et al. Accessory spleen in recurrent chronic immune thrombocytopenic purpura. *Am J Hematol.* 1992;41(3):184-189.
 115. Budzynski A, Bobrzynski A, Sacha T, Skotnicki A. Laparoscopic removal of retroperitoneal accessory spleen in patient with relapsing idiopathic thrombocytopenic purpura 30 years after classical splenectomy. *Surg Endosc.* 2002;16(11):1636.
 116. Balmer P, Falconer M, McDonald P, et al. Immune response to meningococcal serogroup C conjugate vaccine in asplenic individuals. *Infect Immun.* 2004;72(1):332-337.
 117. de Montalembert M, Lenoir G. Antibiotic prevention of pneumococcal infections in asplenic hosts: admission of insufficiency. *Ann Hematol.* 2004; 83(1):18-21.
 118. No authors listed. Guidelines for the prevention and treatment of infection in patients with an absent or dysfunctional spleen. Working Party of the British Committee for Standards in Haematology Clinical Haematology Task Force. *BMJ.* 1996; 312(7028):430-434.
 119. Center for Disease Control. Recommendations of the Advisory Committee on Immunization Practices (ACIP): use of vaccines and immunoglobulins in persons with altered immunocompetence. *MMWR.* 1993;42(RR-4):1-18.
 120. McMullin M, Johnston G. Long term management of patients after splenectomy. *BMJ.* 1993; 307(6916):1372-1373.
 121. Makris M, Greaves M, Winfield DA, Preston FE, Lilleyman JS. Long-term management after splenectomy. Lifelong penicillin unproved in trials. *BMJ.* 1994;308(6921):131-132.
 122. Kaplinsky C, Spirer Z. Post-splenectomy antibiotic prophylaxis—unfinished story: to treat or not to treat? *Pediatr Blood Cancer.* 2006;47(5 suppl): 740-741.
 123. Newland A, Provan D, Myint S. Preventing severe infection after splenectomy. *BMJ.* 2005;331(7514):417-418.
 124. Mathias SD, Bussel JB, George JN, et al. A disease-specific measure of health-related quality of life for use in adults with immune thrombocytopenic purpura: its development and validation. *Health Qual Life Outcomes.* 2007;5:11.
 125. Mathias SD, Gao SK, Miller KL, et al. Impact of chronic Immune Thrombocytopenic Purpura (ITP) on health-related quality of life: a conceptual model starting with the patient perspective. *Health Qual Life Outcomes.* 2008;6:13.
 126. McMillan R, Bussel JB, George JN, Lalla D, Nichol JL. Self-reported health-related quality of life in adults with chronic immune thrombocytopenic purpura. *Am J Hematol.* 2008;83(2):150-154.
 127. Psaila B, Bussel JB. Refractory immune thrombocytopenic purpura: current strategies for investigation and management. *Br J Haematol.* 2008; 143(1):16-26.
 128. Figueroa M, Gehlsen J, Hammond D, et al. Combination chemotherapy in refractory immune thrombocytopenic purpura. *N Engl J Med.* 1993; 328(17):1226-1229.
 129. McMillan R. Long-term outcomes after treatment for refractory immune thrombocytopenic purpura. *N Engl J Med.* 2001;344(18):1402-1403.
 130. Willis F, Marsh JC, Bevan DH, et al. The effect of treatment with Campath-1H in patients with autoimmune cytopenias. *Br J Haematol.* 2001;114(4): 891-898.
 131. Zaydan MA, Turner C, Miller AM. Resolution of chronic idiopathic thrombocytopenia purpura following syngeneic peripheral blood progenitor transplant. *Bone Marrow Transplant.* 2002;29(1): 87-89.
 132. Butler JP, Durrant ST, Frost T. Successful remission of chronic, refractory autoimmune thrombocytopenic purpura following non-myceloablative allogeneic stem cell transplantation. *Bone Marrow Transplant.* 2003;31(7):621-622.
 133. Passweg JR, Rabusin M. Hematopoietic stem cell transplantation for immune thrombocytopenia and other refractory autoimmune cytopenias. *Autoimmunity.* 2008;41(8):660-665.
 134. Huhn RD, Fogarty PF, Nakamura R. High-dose cyclophosphamide with autologous lymphocyte-depleted peripheral blood stem cell (PBSC) support for treatment of refractory chronic autoimmune thrombocytopenia. *Blood.* 2003;101(1):71-77.
 135. Lete I, Bispo C, Izaguirre F, et al. The levonorgestrel intrauterine system (Mirena) for treatment of idiopathic menorrhagia. Assessment of quality of life and satisfaction. *Eur J Contracept Reprod Health Care.* 2008;13(3):231-237.
 136. Matthews JH, Benjamin S, Gill DS, Smith NA. Pregnancy-associated thrombocytopenia: definition, incidence and natural history. *Acta Haematol.* 1990;84(1):24-29.
 137. Gill KK, Kelton JG. Management of idiopathic thrombocytopenic purpura in pregnancy. *Semin Hematol.* 2000;37(3):275-289.
 138. Won YW, Moon W, Yun YS, et al. Clinical aspects of pregnancy and delivery in patients with chronic idiopathic thrombocytopenic purpura (ITP). *Korean J Intern Med.* 2005;20(2):129-134.
 139. Fujimura K, Harada Y, Fujimoto T, et al. Nationwide study of idiopathic thrombocytopenic purpura in pregnant women and the clinical influence on neonates. *Int J Hematol.* 2002;75(4):426-433.
 140. Calderwood C. Thromboembolism and thrombophilia in pregnancy. *Curr Obstet Gynaecol.* 2006; 16:321-326.
 141. Samuels P, Bussel JB, Braitman LE, et al. Estimation of the risk of thrombocytopenia in the offspring of pregnant women with presumed immune thrombocytopenic purpura. *N Engl J Med.* 1990;323(4):229-235.
 142. Veneri D, Franchini M, Raffaelli R, et al. Idiopathic thrombocytopenic purpura in pregnancy: analysis of 43 consecutive cases followed at a single Italian institution. *Ann Hematol.* 2006;85(8):552-554.
 143. Letsky EA, Greaves M. Guidelines on the investigation and management of thrombocytopenia in pregnancy and neonatal alloimmune thrombocytopenia. Maternal and Neonatal Haemostasis Working Party of the Haemostasis and Thrombosis Task Force of the British Society for Haematology. *Br J Haematol.* 1996;95(1):21-26.
 144. Rolbin SH, Abbott D, Musclow E, et al. Epidural anesthesia in pregnant patients with low platelet counts. *Obstet Gynecol.* 1988;71(6 pt 1):918-920.
 145. Beilin Y, Zahn J, Comerford M. Safe epidural analgesia in thirty parturients with platelet counts between 69,000 and 98,000 mm(-3). *Anesth Analg.* 1997;85(2):385-388.
 146. Rasmus KT, Rottman RL, Kotenko DM, et al. Unrecognized thrombocytopenia and regional anesthesia in parturients: a retrospective review. *Obstet Gynecol.* 1989;73(6):943-946.
 147. Michel M, Novoa MV, Bussel JB. Intravenous anti-D as a treatment for immune thrombocytopenic purpura (ITP) during pregnancy. *Br J Haematol.* 2003;123(1):142-146.
 148. Sieunarine K, Shapiro S, Al Baidi MJ, Girling J. Intravenous anti-D immunoglobulin in the treatment of resistant immune thrombocytopenic purpura in pregnancy. *BJOG.* 2007;114(4):505-507.
 149. Erkmann J, Blythe JG. Azathioprine therapy complicated by pregnancy. *Obstet Gynecol.* 1972; 40(5):708-710.
 150. Price HV, Salaman JR, Laurence KM, Langmaid H. Immunosuppressive drugs and the foetus. *Transplantation.* 1976;21(4):294-298.
 151. Alstead EM, Ritchie JK, Lennard-Jones JE, Farthing MJ, Clark ML. Safety of azathioprine in pregnancy in inflammatory bowel disease. *Gastroenterology.* 1990;99(2):443-446.
 152. Christiaens GC, Nieuwenhuis HK, von dem Borne AE, et al. Idiopathic thrombocytopenic purpura in pregnancy: a randomized trial on the effect of antenatal low dose corticosteroids on neonatal platelet count. *Br J Obstet Gynaecol.* 1990; 97(10):893-898.
 153. Reindl W, Schmid RM, Huber W. Cyclosporin A treatment of steroid-refractory ulcerative colitis during pregnancy: report of two cases [letter]. *Gut.* 2007;56(7):1019.
 154. Reddy D, Murphy SJ, Kane SV, Present DH, Kornbluth AA. Relapses of inflammatory bowel disease during pregnancy: in-hospital management and birth outcomes. *Am J Gastroenterol.* 2008;103(5):1203-1209.
 155. Kaplan C, Daffos F, Forestier F, et al. Fetal platelet counts in thrombocytopenic pregnancy. *Lancet.* 1990;336(8727):979-982.
 156. Bussel JB, Druzin ML, Cines DB, Samuels P. Thrombocytopenia in pregnancy [letter]. *Lancet.* 1991;337(8735):251.
 157. Burrows RF, Kelton JG. Pregnancy in patients with idiopathic thrombocytopenic purpura: assessing the risks for the infant at delivery. *Obstet Gynecol Surv.* 1993;48(12):781-788.
 158. Bussel J, Kaplan C, McFarland J. Recommendations for the evaluation and treatment of neonatal autoimmune and alloimmune thrombocytopenia. The Working Party on Neonatal Immune Thrombocytopenia of the Neonatal Hemostasis Subcommittee of the Scientific and Standardization Committee of the ISTH. *Thromb Haemost.* 1991; 65(5):631-634.
 159. Christensen RD, Henry E, Wiedmeier SE, et al. Thrombocytopenia among extremely low birth weight neonates: data from a multihospital healthcare system. *J Perinatol.* 2006;26(6):348-353.
 160. Boehlen F, Hohfeld P, Extermann P, de MP. Maternal antiplatelet antibodies in predicting risk of neonatal thrombocytopenia. *Obstet Gynecol.* 1999;93(2):169-173.
 161. Scioscia AL, Grannum PA, Copel JA, Hobbins JC. The use of percutaneous umbilical blood sampling in immune thrombocytopenic purpura. *Am J Obstet Gynecol.* 1988;159(5):1066-1068.
 162. Scott JR, Cruikshank DP, Kochenour NK, Pitkin RM, Warenski JC. Fetal platelet counts in the obstetric management of immunologic thrombocytopenic purpura. *Am J Obstet Gynecol.* 1980; 136(4):495-499.
 163. Adams DM, Bussel JB, Druzin ML. Accurate intrapartum estimation of fetal platelet count by fetal scalp samples smear. *Am J Perinatol.* 1994; 11(1):42-45.

164. Bussel JB. Immune thrombocytopenia in pregnancy: autoimmune and alloimmune. *J Reprod Immunol.* 1997;37(1):35-61.
165. Douglas MJ. The use of neuraxial anesthesia in parturients with thrombocytopenia: what is an adequate platelet count? In: Halpern SH, Douglas MJ, eds. *Evidence-Based Obstetric Anesthesia*. Malden, MA: Blackwell; 2005.
166. Greaves M, Letsky EA. Guidelines on the investigation and management of thrombocytopenia in pregnancy and neonatal alloimmune thrombocytopenia. *Br J Obstet Gynaecol.* 1997;104(10):1108.
167. Hunt BJ, Lyons G. Thromboelastography should be available in every labour ward. *Int J Obstet Anesth.* 2005;14(4):324-325.
168. Bader-Meunier B, Proulle V, Trichet C, et al. Misdiagnosis of chronic thrombocytopenia in childhood. *J Pediatr Hematol Oncol.* 2003;25(7):548-552.
169. Kottayam R, Rozenberg G, Brighton T, Cohn RJ. Isolated thrombocytopenia in children: thinking beyond idiopathic thrombocytopenic purpura and leukaemia. *J Paediatr Child Health.* 2007;43(12):848-850.
170. Kalpathi R, Bussel JB. Diagnosis, pathophysiology and management of children with refractory immune thrombocytopenic purpura. *Curr Opin Pediatr.* 2008;20(1):8-16.
171. Imbach P, Kuhne T, Muller D, et al. Childhood ITP: 12 months follow-up data from the prospective registry I of the Intercontinental Childhood ITP Study Group (ICIS). *Pediatr Blood Cancer.* 2006;46(3):351-356.
172. Klaassen RJ, Doyle JJ, Krahn MD, Blanchette VS, Nagle G. Initial bone marrow aspiration in childhood idiopathic thrombocytopenia: decision analysis. *J Pediatr Hematol Oncol.* 2001;23(8):511-518.
173. Bolton-Maggs PH, Moon I. Assessment of UK practice for management of acute childhood idiopathic thrombocytopenic purpura against published guidelines. *Lancet.* 1997;350(9078):620-623.
174. Bolton-Maggs P, Moon I. National audit of the management of childhood idiopathic thrombocytopenic purpura against UK guidelines: closing the loop – education and re-audit demonstrate a change in practice [abstract]. *Blood.* 2001;98:58b.
175. Sutor AH, Harms A, Kaufmehl K. Acute immune thrombocytopenia (ITP) in childhood: retrospective and prospective survey in Germany. *Semin Thromb Hemost.* 2001;27(3):253-267.
176. Zeller B, Helgestad J, Hellebostad M, et al. Immune thrombocytopenic purpura in childhood in Norway: a prospective, population-based registration. *Pediatr Hematol Oncol.* 2000;17(7):551-558.
177. Neunert CE, Bright BC, Buchanan GR. Severe chronic refractory immune thrombocytopenic purpura during childhood: a survey of physician management. *Pediatr Blood Cancer.* 2008;51(4):513-516.
178. Butros LJ, Bussel JB. Intracranial hemorrhage in immune thrombocytopenic purpura: a retrospective analysis. *J Pediatr Hematol Oncol.* 2003;25(8):660-664.
179. Lilleyman JS. Intracranial haemorrhage in idiopathic thrombocytopenic purpura. Paediatric Haematology Forum of the British Society for Haematology. *Arch Dis Child.* 1994;71(3):251-253.
180. Lilleyman JS. Intracranial hemorrhage in chronic childhood ITP [editorial]. *Pediatr Hematol Oncol.* 1997;14(5):iii-iv.
181. Buchanan GR, Adix L. Grading of hemorrhage in children with idiopathic thrombocytopenic purpura. *J Pediatr.* 2002;141(5):683-688.
182. Neunert CE, Buchanan GR, Imbach P, et al. Severe hemorrhage in children with newly diagnosed immune thrombocytopenic purpura. *Blood.* 2008;112(10):4003-4008.
183. Klaassen RJ, Blanchette VS, Barnard D, et al. Validity, reliability, and responsiveness of a new measure of health-related quality of life in children with immune thrombocytopenic purpura: the Kids' ITP Tools. *J Pediatr.* 2007;150(5):510-515, 515.e1.
184. Buchanan GR, de Alarcon PA, Feig SA, et al. Acute idiopathic thrombocytopenic purpura—management in childhood. *Blood.* 1997;89(4):1464-1465.
185. Dickerhoff R, von RA. The clinical course of immune thrombocytopenic purpura in children who did not receive intravenous immunoglobulins or sustained prednisone treatment. *J Pediatr.* 2000;137(5):629-632.
186. Bolton-Maggs PH, Dickerhoff R, Vora AJ. The nontreatment of childhood ITP (or “the art of medicine consists of amusing the patient until nature cures the disease”). *Semin Thromb Hemost.* 2001;27(3):269-275.
187. Blanchette V, Imbach P, Andrew M, et al. Randomised trial of intravenous immunoglobulin G, intravenous anti-D, and oral prednisone in childhood acute immune thrombocytopenic purpura. *Lancet.* 1994;344(8924):703-707.
188. El Alfy MS, Mokhtar GM, El-Laboudy MA, Khalifa AS. Randomized trial of anti-D immunoglobulin versus low-dose intravenous immunoglobulin in the treatment of childhood chronic idiopathic thrombocytopenic purpura. *Acta Haematol.* 2006;115(1-2):46-52.
189. Roberti I, Bagtas JF, Reisman L, Murphy S. Severe acute renal failure due to hemoglobinuria after use of WinRho for the treatment of idiopathic thrombocytopenic purpura. *Clin Pediatr (Phila).* 2001;40(1):61-62.
190. Alioglu B, Avci Z, Ozyurek E, Ozbek N. Anti-D immunoglobulin-induced prolonged intravascular hemolysis and neutropenia. *J Pediatr Hematol Oncol.* 2007;29(9):636-639.
191. Imbach P, Barandun S, d'Apuzzo V, et al. High-dose intravenous gammaglobulin for idiopathic thrombocytopenic purpura in childhood. *Lancet.* 1981;1(8232):1228-1231.
192. Imbach P. A multicenter European trial of intravenous immune globulin in immune thrombocytopenic purpura in childhood. *Vox Sang.* 1985;49(suppl 1):25-31.
193. Hedlund-Treutiger I, Henter JI, Elinder G. Randomized study of IVIg and high-dose dexamethasone therapy for children with chronic idiopathic thrombocytopenic purpura. *J Pediatr Hematol Oncol.* 2003;25(2):139-144.
194. Beck CE, Nathan PC, Parkin PC, Blanchette VS, Macarthur C. Corticosteroids versus intravenous immune globulin for the treatment of acute immune thrombocytopenic purpura in children: a systematic review and meta-analysis of randomized controlled trials. *J Pediatr.* 2005;147(4):521-527.
195. Blanchette VS, Luke B, Andrew M, et al. A prospective, randomized trial of high-dose intravenous immune globulin G therapy, oral prednisone therapy, and no therapy in childhood acute immune thrombocytopenic purpura. *J Pediatr.* 1993;123(6):989-995.
196. Benesch M, Kerbl R, Lackner H, et al. Low-dose versus high-dose immunoglobulin for primary treatment of acute immune thrombocytopenic purpura in children: results of a prospective, randomized single-center trial. *J Pediatr Hematol Oncol.* 2003;25(10):797-800.
197. Carcao MD, Zipursky A, Butchart S, Leaker M, Blanchette VS. Short-course oral prednisone therapy in children presenting with acute immune thrombocytopenic purpura (ITP). *Acta Paediatr Suppl.* 1998;424:71-74.
198. Kühne T, Freedman J, Semple JW, et al. Platelet and immune responses to oral cyclic dexamethasone therapy in childhood chronic immune thrombocytopenic purpura. *J Pediatr.* 1997;130(1):17-24.
199. Borgna-Pignatti C, Rugolotto S, Nobili B, et al. A trial of high-dose dexamethasone therapy for chronic idiopathic thrombocytopenic purpura in childhood. *J Pediatr.* 1997;130(1):13-16.
200. Ozsoylu S, Irken G, Karabent A. High-dose intravenous methylprednisolone for acute childhood idiopathic thrombocytopenic purpura. *Eur J Haematol.* 1989;42(5):431-435.
201. Ozsoylu S, Sayli TR, Ozturk G. Oral megadose methylprednisolone versus intravenous immunoglobulin for acute childhood idiopathic thrombocytopenic purpura. *Pediatr Hematol Oncol.* 1993;10(4):317-321.
202. Ozer EA, Yaprak I, Atabay B, et al. Oral cyclic megadose methylprednisolone therapy for chronic immune thrombocytopenic purpura in childhood. *Eur J Haematol.* 2000;64(6):411-415.
203. Wang J, Wiley JM, Luddy R, et al. Chronic immune thrombocytopenic purpura in children: assessment of rituximab treatment. *J Pediatr.* 2005;146(2):217-221.
204. Bennett CM, Rogers ZR, Kinnamon DD, et al. Prospective phase 1/2 study of rituximab in childhood and adolescent chronic immune thrombocytopenic purpura. *Blood.* 2006;107(7):2639-2642.
205. Parodi E, Nobili B, Perrotta S, et al. Rituximab (anti-CD20 monoclonal antibody) in children with chronic refractory symptomatic immune thrombocytopenic purpura: efficacy and safety of treatment. *Int J Hematol.* 2006;84(1):48-53.
206. Aronis S, Platokouki H, Avgeri M, Pergantou H, Keramidas D. Retrospective evaluation of long-term efficacy and safety of splenectomy in chronic idiopathic thrombocytopenic purpura in children. *Acta Paediatr.* 2004;93(5):638-642.
207. Kühne T, Blanchette V, Buchanan GR, et al. Splenectomy in children with idiopathic thrombocytopenic purpura: a prospective study of 134 children from the Intercontinental Childhood ITP Study Group. *Pediatr Blood Cancer.* 2007;49(6):829-834.