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

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Running title: Diagnosis and treatment of immune thrombocytopenia

Abstract

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, children and in pregnancy. The inclusion of summary tables within this document, supported by information tables in the online appendices, is intended to aid clinical decision making.

Introduction

Primary immune thrombocytopenia (ITP) is an acquired immune-mediated disorder characterized by isolated thrombocytopenia, defined as a peripheral blood platelet count $<100 \times 10^9/L$, and the absence of any obvious initiating and/or underlying cause of the thrombocytopenia.¹ Until recently, the initials 'ITP' stood for 'idiopathic thrombocytopenic purpura', but current awareness relating to the immune-mediated nature of the disease, as well as 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 where both impaired platelet production and T-cell-mediated effects play a role.**²⁻⁶ Recent epidemiological data suggest that the incidence in adults is approximately equal for gender except in the mid-adult years (30–60 years), where 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 While 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, while 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 (e.g. age, lifestyle factors,

uremia, etc.) affect the risk and should be evaluated before deciding on the appropriate management.

The investigation and management of ITP patients vary widely. The purpose of this consensus document is to comment upon new data and provide recommendations relating to diagnosis and treatment. Final judgment regarding care of individual patients should, however, lie with the responsible healthcare 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 (USA 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 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 in order 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) meetings 2003–2007 were also reviewed for relevance. Papers were graded using a specific scoring system (Appendix I). Levels of evidence were reviewed by the lead writing committee at two 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 online.

Diagnostic approach in patients with suspected ITP (Supplementary recommendation box 1)

Diagnostic tools for adults and children with suspected ITP were grouped into three sections of recommendation (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, e.g. 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 about 60% of pediatric cases, there is a history of a prior 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 longstanding 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 presenting 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.

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 is due to 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 which 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 (Appendix IX). 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 >60 years of age, those with systemic symptoms or abnormal signs or in some cases where splenectomy is considered.¹⁵⁻¹⁸ Both a bone marrow aspirate and 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 those 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 impact.²⁰ (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 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. While 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.

Anti-nuclear antibodies

A positive anti-nuclear antibody (ANA) test may be a predictor of chronicity in childhood ITP²⁶ (Evidence level IIb).

Anti-thyroid antibody and thyroid function testing

8-14% 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, e.g., 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.

Management of adult ITP

Although RCT data are now available for some new ITP treatments (e.g. romiplostim, eltrombopag), only a limited number of RCTs have been conducted in adults using traditional therapies and even fewer for other agents. While 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 hemorrhage to be 0.0162–0.0389 cases per adult patient-year at risk.²⁸ Patients >60 years and those with prior 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: bleeding due to platelet dysfunction or another hemostatic defect, trauma, surgery,³¹ clearly identified comorbidities for bleeding, mandated anticoagulation therapy or individuals 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 (Supplementary recommendation box 2).

First-line treatment (initial treatment for newly diagnosed patients [Supplementary recommendation box 3])

Response rate criteria vary between studies 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 0.5–2 mg/kg/day until the platelet count increases ($\geq 30\text{--}50 \times 10^9/\text{L}$), which may require several days to several weeks^{9,36,37} Although 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 abandoned in the treatment of chronic refractory ITP patients^{39,40} recent results from two 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 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, direct antiglobulin test (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 splenectomy.⁴⁸⁻⁵⁰ Two studies have demonstrated that IV anti-D administered at 75 µg/kg, instead of the licensed 50 µg/kg dose, increases the platelet count comparable to IVIg.^{51,52} Premedication with paracetamol/acetaminophen, or corticosteroids (e.g. 20 mg 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.

Intravenous immunoglobulin (IVIg)

Numerous controlled trials have been performed with high dose IVIg, since its initial use ~20 years ago,⁵⁴ and have shown initial response rates comparable to 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 0.3–0.4 g/kg every 3–4 weeks.⁵⁵

Although 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/day over 5 days).⁵⁶ Rare, but serious, toxicities include renal failure and thrombosis.^{57;58} The fear of transmission of infectious disease persists but there is no recent evidence for transmission of HIV, HCV and HCB, 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 (Supplementary recommendation box 4)

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.

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.⁵⁹ 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 where oral anti-coagulation or anti-platelet medication is necessary (e.g. patients with cardiac stents requiring aspirin and/or clopidogrel) and necessitates raising the threshold platelet count for treatment. In patients with reduced renal function, hemostasis may be improved with desmopressin and by maintaining hemoglobin ≥ 10 g/dL.

Platelet transfusions with or without IVIg

Platelet transfusion increases the post-transfusion platelet count by over 20×10^9 /L in 42% of bleeding ITP patients and may reduce bleeding.⁶⁰ In a retrospective study of 40 patients⁵⁹ (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 treatment⁶¹ (Evidence level IIb).

Emergency splenectomy

See Splenectomy section

Anti-fibrinolytics

Anti-fibrinolytic agents, such as oral or IV tranexamic acid and epsilon-aminocaproic acid may be useful to prevent recurrent bleeding in patients with severe thrombocytopenia; however the efficacy has not been evaluated by randomized trial in ITP patients. Tranexamic acid (1 g three times daily orally) and epsilon-aminocaproic acid (1–4 g, every 4–6 hours [maximum dose 24 g/day]) 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 response⁶² (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, other active comorbidities, and to the understanding that spontaneous improvement or late remission may occur 6–12 months after diagnosis; indeed, some patients may spontaneously remit even years after diagnosis.

Second-line therapy – medical (Supplementary recommendation box 5)

Treatment options are listed alphabetically so as to show no preference for a particular therapy-(Table 5).

Azathioprine

Despite little 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 per day) for a median of 18 months.⁶³ 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 patients⁶⁴ (Evidence level III).

Cyclosporin A

Cyclosporin A (2.5–3 mg/kg/day) 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 (e.g. older patients and those with renal insufficiency). Clinical improvement was observed in >80% of patients resistant to first-line therapy, with 42% achieving a complete response⁶⁵ (Evidence level IIa). Remissions may be durable (mean 29 months) following discontinuation of treatment⁶⁶ (Evidence level IIb). Side effects are usually moderate but transient and include fatigue, renal insufficiency, hypertension and neuropathy.⁶⁵

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 24–85%^{43;67;68} and toxicity was mild to moderate.⁶⁸ However, there are reports of ITP and systemic lupus erythematosus (SLE) patients developing acute myeloid leukemia (AML) after cyclophosphamide therapy.⁶⁹ 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, 2–4 times daily (10–15 mg/kg/day). Response rates of 60–67% have been recorded (>50x10⁹/L for ≥2 months in 57 ITP patients post-splenectomy).⁷⁰ Older females and splenectomized patients may have the highest response.⁷⁰

Dapsone

Dapsone is a moderate corticosteroid-sparing agent that is usually administered orally at a dose of 75–100 mg/day.⁷¹ 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 rate⁷²

Male patients at risk for glucose-6-phosphate dehydrogenase (G6PD) deficiency should be screened before starting treatment and monitored for hemolysis and methemoglobinemia⁷³ (Evidence level III).

Mycophenolate mofetil (MMF)

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 bid over 3 weeks) produced platelet increase in 39% of patients with refractory ITP, but was not sustained⁷⁴ (Evidence level IIb). In a retrospective study, the overall response rate was 78% (major response: >80x10⁹/L; and moderate response: 30–80x10⁹/L at 3 months).⁷⁵

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.⁷⁶ Responses generally occur after 1–2 weeks to 6–8 weeks^{77;78} and last from 2 months in partial responders to ≥ 5 years in 15–20% of initially treated patients.⁷⁶ 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 II trial, 33% of patients had a platelet count $\geq 50 \times 10^9/L$ and 40% had a platelet count $\geq 30 \times 10^9/L$ without any additional treatment.⁷⁹ Although the studies above 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.⁸⁰ 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.⁸¹

Rituximab is contraindicated in patients with evidence of active hepatitis B infection (e.g. positive hepatitis B/C core antibody). Adverse events associated with rituximab are usually mild or moderate, with a low incidence of infections.^{78;82} There are also reports of over 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.^{83;84} Hence, additional long-term safety data are required. These 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 production⁸⁵ and several TPO-receptor agonists have been developed that activate the TPO receptor and increase platelet production.⁸⁶⁻⁸⁹ Two agents, romiplostim and eltrombopag, are FDA-approved for the treatment of ITP. Romiplostim is administered as a 1–10 $\mu\text{g/kg}$ subcutaneous weekly injection.^{89;90}

Eltrombopag is an oral non-peptide TPO-receptor agonist administered as a 25, 50 or 75 mg daily dose^{88;90;91} (Evidence level Ib/IIa).

Data from Phase I–III trials have demonstrated that both drugs are highly effective in increasing the platelet count in both healthy volunteers and ITP patients.^{86;88–94} In two parallel, placebo-controlled, double-blind randomized Phase III trials romiplostim was given to 63 splenectomized and 62 non-splenectomized patients for 6 months.⁸⁹ 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.⁸⁹ 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 $\geq 50 \times 10^9/L$ on day 43 of the study.⁹⁰

Across the two romiplostim studies, 87% of romiplostim-treated patients reduced or discontinued concurrent ITP therapy, including corticosteroids and IVIg.⁸⁹ 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 therapy⁹⁴. 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 over 271 patients included in the romiplostim trials and seven of 117 patients in the eltrombopag trials. Long-term studies will address the importance of this finding and whether routine monitoring is required.^{89;94} Although reported in rodent studies with eltrombopag, there was no increase in cataracts observed in the ITP studies.^{88;90;95} Liver function test abnormalities were seen in 13% of eltrombopag-treated patients.⁹⁶

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.⁸⁹

Vinca alkaloids

Vinca alkaloids may cause a transient platelet count increase in two-thirds of patients lasting 1–3 weeks.¹⁵ Approximately 50% of splenectomized patients respond to vinca alkaloids but this is not sustained.^{15;97;98}

Second line therapy – surgical (Supplementary recommendation box 6)

Splenectomy

Eighty percent of patients respond to splenectomy and response is sustained in 66% with no additional therapy for at least 5 years.^{99;100;101} Many patients without a complete response can still expect a partial or transient response.^{15;102} Approximately 14% of patients do not respond and approximately 20% of responders relapse weeks, months or years later⁹⁹ (Evidence level IIb).

Complications of splenectomy

Complications of splenectomy include bleeding, infection, thrombosis, prolonged hospitalization, readmission to the hospital, or requirement for additional intervention.¹⁰⁰ Reported complication rates vary considerably,^{30;99;100;103;104} and may be greater in patients aged ≥ 65 years.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.¹⁰⁰

Since ITP²² and splenectomy¹⁰⁵ are both associated with thromboembolic risks, ITP patients should receive appropriate post-operative 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^{106;107} (Evidence level IIb). Indium-labeled autologous platelet scanning may be the most sensitive predictor of response to splenectomy, but here too studies vary.^{108;109} When scanning reveals splenic platelet destruction, ~90% respond to splenectomy.¹⁰⁸ This test is currently limited to several research centers, but if available may be useful prior to 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 are removed during surgery.¹¹⁰ 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;111}

Prevention of infection post-splenectomy

Splenectomized patients are at life-long risk for uncontrolled infection with a poor outcome from *Streptococcus pneumoniae*, *Neisseria meningitidis* and *Haemophilus influenzae*.^{112;113}

Patients are usually given prophylactic polyvalent pneumococcal, meningococcal C conjugate and *Haemophilus influenzae* b (Hib) vaccines at least 4 weeks prior (preferably) to or 2 weeks after splenectomy and revaccinated according to the country-specific recommendations (Evidence level IV).^{114;115} In patients who have received rituximab in the past 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 (bid), or equivalent, or erythromycin 500 mg bid).¹¹⁶ However, the benefit of lifelong antibiotic prophylaxis is unproven^{117;118} and the risk of late infection is quite low and therefore no consensus has been reached.¹¹⁹

A practical policy is for splenectomized patients to have a home supply of antibiotics (e.g. penicillin VK, erythromycin or levofloxacin) for use in case of a febrile illness. Patients should be educated about the risk of post-splenectomy infection including the need to go to the emergency department if fever >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 patients failing first- and second-line therapies [Supplementary recommendation box 7])

Patients failing first- and second-line therapies

Approximately 20% of patients do not attain a hemostatic platelet count post-splenectomy or after first- and second-line medical approaches; an additional 10–20% of splenectomy responders eventually relapse (Evidence level IV). These patients may be able to tolerate severe thrombocytopenia (i.e. platelet counts as low as $10 \times 10^9/L$) relatively well with near normal quality of life. However some have consistent and statistically significant deficits on quality of life measures, bleeding and increased risk of death.^{28;120-122} For those failing standard therapies and still requiring 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.¹²³ 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.^{61;124;125} A combination of cyclophosphamide (100–200 mg/day IV) on days 1–5 or 7 and prednisone (0.5–1.0 mg/kg orally daily) on days 1 to 7, combined with vincristine (1–2 mg IV) on day 1, and one of the following: azathioprine (100 mg orally daily) on days 1 to 5 or 7 or etoposide (50 mg orally daily) on days 1–7 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 ITP,¹²⁶ 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 (HSCT)

Remissions have been induced in some patients with chronic refractory ITP using autologous or allogeneic hematopoietic stem cell transplantation (HSCT)¹²⁷⁻¹³⁰ (Evidence level IIb/III). However, potentially fatal toxicities such as neutropenic fever, cerebral hemorrhage and septicemia may occur.¹²⁹ HSCT is warranted only in patients with 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 79% approximate overall response rate^{86;88-90;94} (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 their apparent low toxicity and good tolerability 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.⁹⁴

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

Anti-fibrinolytics

See Emergency treatment section (Evidence level IV)

Inhibition of menstrual bleeding

Both progesterone-containing intrauterine contraceptive device and oral contraceptives can decrease the frequency and amount of menstrual bleeding¹³¹ (Evidence level IIb).

Other measures

Patient groups (including <http://www.itpsupport.org.uk/>; <http://www.pdsa.org/>; <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 non-pregnant women.¹³² This gestational thrombocytopenia is caused by a combination of hemodilution and increased platelet activation and clearance. A decrease of ~10% in platelet count is typical towards the end of the third trimester. ITP is estimated to occur in 1 in 1000 to 1 in 10,000 pregnant women.¹³³ Women with previously diagnosed ITP may experience exacerbation or relapse.^{134;135}

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 delivery¹³⁶ due to increased levels of fibrinogen, factor VIII and von Willebrand factor, suppressed fibrinolysis and a reduction in the activity of Protein S.¹³⁶ These changes may result in fewer bleeding symptoms and therefore a greater tolerance to ITP in pregnancy 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 Appendix IX). 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, pre-eclampsia, HELLP syndrome, DIC, folate deficiency, massive obstetrical hemorrhage, acute fatty liver, antiphospholipid antibody syndrome.

Laboratory investigations for the diagnosis of ITP in pregnancy (Supplementary recommendation box 8)

Bone marrow examination is not required to make the diagnosis of ITP in pregnancy. The measurement of maternal anti-platelet 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 between the obstetrician experienced in the management of ITP, the hematologist, obstetric anesthetist and 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.^{134;137;138} Since platelet counts may fall in the third trimester, the frequency of platelet count measurement increases to assist 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 two trimesters, treatment is initiated when a) the patient is symptomatic, b) when platelet counts fall below $20-30 \times 10^9/L$; or c) to produce an increase in platelet count to a level considered safe for procedures. Patients with platelet counts $\geq 20-30 \times 10^9/L$ do not routinely require treatment. They should be monitored more closely as delivery approaches.¹³⁹

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.¹⁴⁰⁻¹⁴² Obstetric anesthetists generally recommend a platelet count $\geq 75 \times 10^9/L$ to allow administration of spinal or epidural anesthesia. Hematologists believe that a platelet count of $\geq 50 \times 10^9/L$ is adequate to allow for Cesarean section.

Recommended treatment options for the management of ITP in pregnancy (Supplementary recommendation box 9)

Primary treatment options for maternal ITP are similar to those of other adult ITP patients. Corticosteroids and IVIg are the first-line treatments for maternal ITP.¹³⁹ The limited evidence for the use of IV anti-D^{143;144}, splenectomy and azathioprine¹⁴⁵⁻¹⁴⁷ is

presented in the following sections. Vinca alkaloids, rituximab, danazol, TPO receptor agonists and most immunosuppressive drugs (other than azathioprine) should not be used in pregnancy because of possible teratogenicity.

First-line treatment (Initial treatment for newly diagnosed patients)

Corticosteroids

Prednisone at a low dose (10–20 mg/day) 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 prior to 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 betamethasone orally per day) on the fetal platelet count¹⁴⁸ (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 50–75 µg/kg has been shown to be effective and safe for both mother and fetus in the second and third trimester^{143;144} (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 $50 \times 10^9/L$.¹⁴³ 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 prior to delivery (Evidence Level IV). HDMP (1000 mg) possibly in combination with IVIg or azathioprine have been suggested as a treatment for pregnant patients refractory to oral corticosteroids or IVIg¹³⁹ (Evidence Level III). Data available for azathioprine in systemic lupus erythematosus and renal transplantation show that it is safe in pregnancy¹⁴⁵⁻¹⁴⁷ (Evidence Level III), however response is slow. Cyclosporin A has not been associated with significant toxicity to mother or fetus during pregnancy.^{149;150}

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.

Pre-pregnancy 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 (Supplementary recommendation box 10)

Historically, management of delivery in mothers with ITP has been dominated by concerns over the risk of severe neonatal thrombocytopenia and hemorrhage. In 1976, Cesarean section was recommended for all ITP patients based on a reported perinatal mortality of 12–21%, 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 <1%.¹³⁷ Large prospective studies published in the 1990s documented an incidence of 'severe' neonatal thrombocytopenia ($<50 \times 10^9/L$) of 8.9–14.7%, with ICH occurring in 0–1.5% of infants with neonatal thrombocytopenia.^{137;151-153} 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 24–48 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.^{139;154}

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.¹³³ In low birth weight neonates admitted to intensive care, thrombocytopenia develops in 18–35% of admissions, and is most common in the smallest individuals¹⁵⁵ (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^{137;139;156} (Evidence Level III). Fetal blood sampling by cordocentesis¹⁵⁷ carries a fetal mortality risk of 1–2% (at least as high as the risk of ICH). Scalp blood sampling in early labor to measure fetal platelet count¹⁵⁸ 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.¹⁵⁹ Attempts to measure the fetal platelet count prior to 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 a) fetal scalp electrodes, b) fetal blood samples, c) ventouse delivery and d) rotational forceps (Evidence Level IV).

After delivery, a cord blood platelet count should be determined¹⁵³ (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 day 2 and 5 after birth. Transcranial ultrasonography should be performed on neonates with platelet counts $<50 \times 10^9/L$ at delivery (Evidence level IV). Although treatment of the neonate is rarely required, in those with clinical hemorrhage or platelet counts $<20 \times 10^9/L$, 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 4–6 weeks after birth. In alloimmune thrombocytopenia, fetal thrombocytopenia tends to worsen in subsequent pregnancies.¹⁶⁰ In ITP the second fetus is usually as affected as the first (Evidence level III).

Obstetric analgesia and anesthesia (Supplementary recommendation box 11)

The decision about regional anesthesia is ideally made predelivery in conjunction with the obstetric anesthesiologist. The general trend in recent years has been to lower the 'cut-off point' to $75\text{--}100 \times 10^9/\text{L}$.¹⁴¹ 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.¹⁶¹

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 anesthesiologists agree no changes to routine practice are required until the platelet count drops below $50 \times 10^9/\text{L}$. For lower counts a careful analysis of benefit against risk of epidural hematoma is needed, and multi-disciplinary discussion 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 those with low but stable levels¹⁶²

Some maternity units have access to thromboelastography or other point-of-care global hemostasis monitoring.¹⁶³ 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 validated¹⁶³ (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 (Supplemental recommendation box 12)

The diagnosis of ITP in children is one of exclusion (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 <http://www.itpsupport.org.uk>; <http://www.pdsa.org/>; www.itp.foundation.org).

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.^{164,165} Inherited disorders should be suspected if thrombocytopenia has been present since early life, a positive family history for a similar disorder is elicited¹⁶⁶ or characteristic features are present.

Special diagnostic considerations in children

Older children are more likely to have chronic disease¹⁶⁷ (Evidence level III). Other autoimmune diseases associated with thrombocytopenia, including SLE, CVID and autoimmune lymphoproliferative syndrome (ALPS [although difficult to assess in

some instances]) 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 only recommended when abnormalities are present other than isolated thrombocytopenia in the blood count/smear, if systemic features (e.g. 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.¹⁶⁸

Helicobacter pylori infection, anti-nuclear antibodies (ANA), antiphospholipid antibodies (APLA) including Lupus anticoagulant (LAC)

(See adult section).

Examination of patients with persistent/early refractory ITP

For patients with an initial diagnosis of ITP and no improvement in platelet count after 3–6 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 bleeding¹⁶⁹⁻¹⁷³ (Evidence level IIb/III). Severe bleeding is more likely in children with platelet counts $<10 \times 10^9/L$ ¹⁷⁴ (Evidence level III). The incidence of intracranial hemorrhage (ICH) in children with ITP is approximately 0.1–0.5%^{167,175,176} (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 co-existing 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.

Clinical classification (Supplementary recommendation box 13)

Classification of children with ITP by severity of bleeding is useful to guide management (Table 8).

Three bleeding scores confirm that most children with ITP do not have serious bleeding problems despite very low platelet counts.^{169;177;178} Of note, the severity of mucocutaneous bleeding does not predict the risk for life-threatening bleeding (e.g. 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 (HRQoL) 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 properties¹⁷⁹ (Evidence level IIa).

Expectant 'watch and wait' policy (Supplementary recommendation box 14)

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^{169-171;178;180-182} (Evidence levels II–IV). 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 that have clinically significant bleeding. Problematic psychosocial circumstances of child and family (e.g. 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 levels IV, Grade C recommendation [Supplementary recommendation box 15]).

Most children with minor, mild or moderate symptoms can be safely managed as outpatients with judicious use of supportive care (e.g. antifibrinolytic agents, oral contraceptives etc.) 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.

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 ($>20\text{--}30 \times 10^9/\text{L}$) 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* in adult section). 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 $10\text{--}30 \times 10^9/\text{L}$ 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 (Supplementary 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;183;184} 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;185;186}

Intravenous immunoglobulin (IVIg)

IVIg raises the platelet count in more than 80% of children and does so more rapidly than corticosteroids or no therapy¹⁸⁷⁻¹⁹⁰ (Evidence level Ia/Ib). Transient side effects (fever, headache, nausea/vomiting) are highest with a dose of 1 g/kg given on consecutive days¹⁹¹ (Evidence level Ia–III).

The original IVIg dose of 0.4 g/kg daily for 2–5 days has been superseded by short course with a single dose of 0.8–1 g/kg, with possible repeat treatment based on the short-term platelet response^{47;192} (Evidence level 1b).

Predniso(lo)ne/corticosteroids

Prednisone at a dose of 1–2 mg/kg/day may be effective at inducing a response in children^{15;16} (Evidence Level Ib). Higher doses (4 mg/kg/day) for 3–4 days have been shown to be effective in up to 72–88% of children (platelet count $>50 \times 10^9/L$) within 72 hours^{183;191;193} (Evidence Level Ib/III).

Owing to 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 (Supplementary recommendation box 17)

In organ- or life-threatening situations (as with adult patients) a larger than usual dose (two-to-three fold) of platelets should be infused together with IV high-dose corticosteroids and IVIg or IV anti-D. The goal of treatment is to elevate the platelet count to a level where the risk of 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 (Supplementary recommendation box 18)

The goal of treatment for children with persistent or chronic ITP is to maintain a hemostatic platelet count with first-line therapies (e.g. IVIg, IV anti-D, short course corticosteroids) and to minimize the use of prolonged corticosteroid therapy. 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/day) has been reported as treatment for patients with refractory ITP.^{194,195} The response rate in previously untreated patients aged <18 years was 86%, with 67% of all evaluable patients reaching platelet levels of $\geq 50 \times 10^9/L$ lasting for a median time of 26 months.³⁶ (Evidence level IIa). However, side effects such as sleeplessness, aggressive behavior and loss of concentration are unacceptably high.¹⁹⁴

High-dose methylprednisolone

HDMP (given as an oral 7-day course of 30 mg/kg/day for 3 days followed by 20 mg/kg/day for 4 days) has been used as an alternative to IVIg¹⁹⁶⁻¹⁹⁸ (Evidence level Ib–III).

IVIg/anti-D

(See first-line/initial therapy in children)

Rituximab (see adult section)

Rituximab has been used with success in children with chronic refractory ITP¹⁹⁹⁻²⁰¹ (Evidence level IIa and IIb). Overall, the response rate ($>50 \times 10^9/L$ platelet count) is between 31–68%. In all case series rituximab was well tolerated with the exception of serum sickness (Appendix table VII).

Single or combination regimens (see adult section)

The experience in children is limited and therefore no recommendations can be made⁶¹ (Evidence level IIb/IV).

TPO-receptor agonists

A number of studies with TPO-receptor agonists have shown encouraging results in adults.^{86,88-94} 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 post-operative risk of infection is a deterrent to its routine use.

Splenectomy (Supplementary recommendation box 19)

Splenectomy with appropriate prior vaccination, followed by prophylactic antibiotics, is an effective treatment for pediatric ITP. 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 post-splenectomy overwhelming sepsis is up to 3% in children.²⁰² 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^{202;203} (Evidence level IIb/III).

Therapies where 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).

Conclusion

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 towards 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.

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Table 1. Recommendations for the diagnosis of ITP in children and adults (See appendix II)

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 – see 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) • Anti-thyroid 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 • PalgG • Bleeding time • Platelet survival study • Serum complement

**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 reassessment evaluation*

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

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

Table 2. Frequent examples of differential diagnosis of ITP and potential alternative causes of thrombocytopenia identified by patient history (See appendix II)

- Previously diagnosed or possible high risk of conditions that may be associated with autoimmune thrombocytopenia, eg human immunodeficiency virus (HIV), hepatitis C virus (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 post-transfusion purpura), and recent immunizations
- Inherited thrombocytopenia: Thrombocytopenia Absent Radius Syndrome (TAR), radioulnar synostosis, congenital amegakaryocytic thrombocytopenia, Wiskott-Aldrich syndrome, MYH9-related disease, Bernard-Soulier syndrome, Type IIB von Willebrand's disease

Table 3. Therapies for the treatment of ITPFrom www.bloodjournal.org at AMGEN MULTI-SITE on October 21, 2009. For personal use only.

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 Thrombopoietin (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 Hemopoietic stem cell transplantation (HSCT)	

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

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	Appendix
Corticosteroids	Dexamethasone 40 mg daily for 4 days every 2–4 weeks for 1 to 4 cycles	Up to 90% of patients respond initially	Several days–several weeks	<p>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.</p> <p>Possibly lower rate of adverse events when used as short-term bolus therapy</p>	As high as 50–80% reported; the latter with 3–6 cycles (during 2–5 years of follow-up)	See appendix III for relevant studies
	Methylprednisolone 30 mg/kg/d for 7 days	As high as 95%	4.7 days vs 8.4 days (high-dose methylprednisolone [HDMP] vs prednisone)		23% patients have sustained platelet count ($>50 \times 10^9/L$) at 39 months	
	Prednis(ol)one 0.5–2 mg/kg/d for 2–4 weeks	70–80% of patients respond initially	Several days–several weeks		Remains uncertain – estimated 10-year disease-free survival 13–15%	
IV Anti-D 50–75 $\mu g/kg$		Initial response rate similar to IVIg (dose dependent)	4–5 days	<p>Common: hemolytic anemia (dose limiting toxicity), fever/chills</p> <p>Rare: intravascular hemolysis, disseminated intravascular coagulation, renal failure, rare</p>	Typically last 3–4 weeks but may persist for months in some patients	

			death		
IVIg* 0.4 g/kg/d for 5 days or Infusions of 1 g/kg/d for 1–2 days	Up to 80% of patients respond initially; half achieve normal platelet counts	Rapid; many respond in 24 hours; typically 2–4 days	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 pre-treatment levels 2–4 weeks following treatment – persists for months in a few patients	

Full details regarding the studies found in the literature search are available in the appendices

*IVIg may be discontinued after 1–2 days if adequate response seen

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	Appendix
Azathioprine 1–2 mg/kg (maximum: 150 mg/day)	Up to two-thirds of patients; 40% in anecdotal reports	Slow – may need to be continued for 3–6 months	Low incidence and generally mild: weakness, sweating, transaminase elevations, severe neutropenia with infection, pancreatitis	Up to a quarter of patients off therapy maintain response	See appendix III for relevant studies
Cyclosporin A 5 mg/kg/day for 6 days 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 weeks	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	Over half of responders receiving low doses sustain remission (at least 2 years)	
Cyclophosphamide (1–2 mg/kg orally daily for at least 16 weeks) or IV (0.3–1 g/m ² for 1–3 doses every 2–4 weeks),	24–85% of patients	1–16 weeks	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 months	Frequent side effects: acne, increased facial hair, increased cholesterol, amenorrhea, transaminitis	46% remained in remission at a median of 119±45 months and mean duration of danazol	

				therapy was 37 months
Dapsone 75–100 mg	Response in up to 50% of patients	3 weeks	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 weeks	Up to 75% of patients – complete response in up to 45%	4–6 weeks	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 x 4 (Lower doses may also be effective)	60% of patients – complete response in 40% of patients	1–8 weeks	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 years in 15–20% of responders. Responders may require retreatment months–years later.
Splenectomy	80% of patients respond. Approximately two-thirds achieve a lasting response	1–24 days	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 over 5–10 years

TPO receptor agonist – eltrombopag 25–75 mg orally daily	Platelet responses (platelet count >50x10 ⁹ /L on day 43 of study): 70% receiving 50 mg dose, 81% receiving 75 mg dose	By day 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 reticulin, worsening thrombocytopenia upon discontinuation, thrombosis, liver function abnormalities in 13%	Up to 1.5 years with continual administration of the drug
TPO receptor agonist – romiplostim Doses 1–10 µg/kg SC weekly	Overall platelet response rate: non-splenectomized: 88% splenectomized: 79%	1–4 weeks (in patients with platelet count <30x10 ⁹ /L to achieve >50x10 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 reticulin, worsening thrombocytopenia upon discontinuation, thrombosis	Up to 4 years 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 alternatively	Highly variable transient response in 10–75% of patients	5–7 days	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 months monitoring; average: 10 months

Further details regarding the studies found in the literature search (2001–2008) are available in the appendices.

Long-term responses for many of these agents are based on fragmented data and potentially poor follow-up

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	Appendix
Category A: treatment options with sufficient data					
TPO receptor agonist – Eltrombopag 25–75 mg orally daily	Platelet responses (platelet count >50x10 ⁹ /L on day 43 of study): 70% receiving 50 mg dose, 81% receiving 75 mg dose	By day 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 years with continual administration of the drug	See appendix III for relevant studies
TPO receptor agonist – Romiplostim 1–10 µg/kg SC weekly	Overall platelet response rate: Non-splenectomized: 88% Splenectomized: 79%	1–4 weeks (in patients with a platelet count <30x10 ⁹ /L to achieve >50x10 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 years with continual 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 week–9 months	Fever, rigors, chills, intracranial hemorrhage, cerebral vein thrombosis, severe intravascular hemolysis, death, infection	All but one patient relapsed within 24 months	See appendix III for relevant studies

Combination chemotherapy: Various regimens see Appendix table III for complete regimen details	Response seen in over two-thirds of patients	2–3 months	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 complete response (CR) (CR in about 40% of all patients)	
Hematopoietic stem cell transplantation	Of 14 patients, 6 achieved remission	5 weeks	Frequent serious toxicities reported in peri- and post-transplant period: infection, mucocutaneous bleeding, myelosuppression, anorexia, graft-versus-host disease (GVHD) and death	Long-term complete remission in one-third of patients. Late (2 years) relapses	

Further details regarding the studies found in the literature search (2001–2008) are available in the appendices

- 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 lupus anticoagulant (LAC)
- Serum immunoglobulins (IgG, IgA, IgM)
- Review of medication usage

Table 8. Grade of severity and management of patients with ITPFrom www.bloodjournal.org at AMGEN MULTI-SITE on October 21, 2009. For personal use only.

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 & Adix¹⁷⁷; Bolton-Maggs & Moon¹⁷⁰; Imbach et al¹

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

Recommended management strategy	Approximate response rate	Approximate time to platelet recovery	Toxicities	Sustained response	Appendix
IV anti-D 50–75 μ g/kg	50–77% achieve a platelet response depending on dose	\geq 50% respond within 24 hours	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	See appendix VII for relevant studies
IVIg single dose of 0.8–1 g/kg on Day 1	Effective in more than 80%	1–2 days	Side effects include: headache which can be severe, fever	Similar to corticosteroids. One-third of patients fall below acceptable platelet counts after 2–6 weeks	
Prednisone conventional dose 1–2 mg/kg/day max 14 days; 4 mg/kg/day for 3–4 days	Up to three quarters (\leq 75%) of patients will respond, depending on dose	2–7 days	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 months	Days to ~6 months	Preventable hemorrhage occurs, activity restriction, anxiety	Spontaneous remissions are generally durable	

Note: 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 adult section)

More complete details regarding the studies found in the literature search (2001–2008) are available in the appendices.

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

Recommended treatment strategy	Approximate response rate	Approximate time to response	Toxicities	Sustained response	Appendix
Dexamethasone 28 mg/m ² /day	Up to 80% achieve a platelet response (study in adults and children)	3 days	Sleeplessness, behavioral changes, hypertension, anxiety, gastric distress, cataract, bronchial pneumonia, fatigue, pain	Responses are of short duration unless cycles are repeated	See appendix for relevant studies
HDMP 30 mg/kg/day for 3 days followed by 20 mg/kg/day for 4 days	At least as effective as IVIg; 60–100% achieve platelet response	2–7 days	Worse side-effect profile compared with prednisone		
Rituximab 100mg or 375 mg/m ² /week for 4 weeks	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 months; however, this is variable in literature	
Single or combination regimens: cyclosporin A, azathioprine, prednisone, IVIg, anti-D, vinca alkaloids and danazol	Approximately 70% 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 hours	Post-splenectomy complications include sepsis	80% of responders maintain platelet response over 4 years	

More complete details regarding the studies found in the literature search (2001–2008) are available in the appendices