A review of the management of childhood immune thrombocytopenia: how can we provide an evidence-based approach?

Nichola Cooper

Department of Haematology, Hammersmith Hospital, Imperial College, London, UK

Summary

Most children with immune thrombocytopenia (ITP) have transiently low platelet counts and do not suffer from bleeding. Treatments with steroids, immunosuppression or splenectomy are not thought to be curative and may create more problems than the low platelet count. Consequently, many children do not receive treatment unless there is bleeding. However, although registry data looks promising, this approach outcome is not consistent between countries, or even between centres in the same country, leading to confusion for both physicians and families. Reaching a consensus for the management of paediatric ITP is further complicated by the lack of a diagnostic test and by the heterogeneity of the disease; for example, although most children remain relatively asymptomatic and go into an early remission, some patients have significant bleeding and others do not go into spontaneous remission. This review assesses the available evidence to guide physicians and families on making management decisions, showing the wide range of treatment choices, and the different approaches between countries and considers methods by which further information could be acquired to provide a more stratified approach to management.

Keywords: paediatric immune thrombocytopenia, splenectomy, thrombocytopenia, thrombopoietin, rituximab.

Platelets are an important part of vascular integrity. Low numbers or impaired quality of platelets increases the risk of bleeding. Depending on the site of the bleed, it can be life threatening, or organ threatening. However, there is poor understanding of what constitutes a safe platelet count.

With the possible exception of splenectomy, most treatments for immune thrombocytopenia (ITP) are not thought to change the course of disease. Furthermore, standard treatments can cause significant adverse effects. For this reason, and because serious bleeds, such as intracranial haemorrhage

(ICH), are rare, there has been an increasing trend not to treat children with ITP.

However, ITP is a heterogeneous disease and there remain many controversies in the management of childhood ITP, such as which children are at risk of bleeding and require immediate treatment, and, if treatment is required, which treatment option should be employed. Furthermore, bleeding risk is not the only concern of a low platelet count. For example, although children may be at low risk of bleeding, low platelet counts can impact other aspects of life, such as loss of socializing, decreased sport activity, anxiety for parents and time lost from school due to clinic reviews and emergency hospital visits. Other roles of the platelet in the vasculature and within the immune system are also unexplored.

Guidelines and consensus statements for the management of ITP are based on very little evidence and are not entirely consistent (George *et al*, 1996; Provan *et al*, 2010; Neunert *et al*, 2011). Some of the differences between the latest documents are described in Table I.

This review will describe the differences in the management of children with ITP between countries. It will consider the available evidence on deciding when to treat children, such as bleeding risks and quality of life-related issues and will evaluate the treatment options for children with ITP. Finally, it will propose methods for addressing areas of uncertainty.

Summary of differences in the management and of children with ITP

The studies outlined in Table II show the wide diversity of treatment decisions between countries, with between 16% and 90% of children receiving treatment for low platelet counts. Some of the differences may reflect changes over time, with less patients being treated in later series. Differences could also reflect differences in presentation, with only more severe patients presenting in certain communities, but also shows a difference in interpretation of the risks of low platelet counts.

Even within individual countries, there is considerable variation in whether patients are treated. A review from the Nordic Society for Pediatric Haematology and Oncology (NOPHO) ITP group separated centres into whether they

Correspondence: Dr Nichola Cooper, Department of Haematology, Hammersmith Hospital, Du Cane Road, London W12 0HS, UK.
E-mail: n.cooper@imperial.ac.uk

Table I. International guidelines and consensus documents for the treatment of immune thrombocytopenia (ITP).

	International Consensus Document (Provan et al, 2010)	American Society of Hematology guidelines (Neunert et al, 2011)
Factors influencing treatment	Circulating platelet count, activity profile, psychosocial issues	Assessment of impact on daily life. How is the patient coping psychologically with a low platelet count
Steroids	Short course	Short course
Rituximab	Has been used with success in children with chronic refractory ITP. Well tolerated	May be considered in children who have significant on going bleeding and/or have a need for improved quality of life despite conventional treatment. May also be considered as an alternative to splenectomy
Immunosuppression	Evidence is limited therefore no recommendation can be made	Multiple agents have been reported; but data for any specific agent remain insufficient for specific recommendations
Splenectomy	Rarely recommended. Post-splenectomy sepsis is up to 3% in children	Chronic or persistent ITP with significant or persistent bleeding and lack of response, or intolerance to other therapies. Should be delayed for at least 12 months, unless disease unresponsive to other measures, or due to quality of life considerations
Thrombopoietin receptor agonists	Insufficient evidence at time of publication. May be of value both for chronic disease and in those not responsive to first line therapies, if safety continues	Insufficient evidence at time of publication

Table II. Variability of treatment rates between countries in children with ITP.

Country	Reference	Review period (years)	Patients (n)	Treatment rates	Morbidity
USA	Kime et al (2013)	2 (2008–2010)	2314	72%	ICH 0·6%
Nordic countries	Rosthoj et al (2012)	5	96		ICH 1%
UK	Grainger et al (2012)	5	225	16%*	ICH 0·5%
Japan	Shirahata et al (2009)	5	986	64%	
South Africa	Paling and Stefan (2008)	10	106	81%	ICH 3%
Italy	Del Vecchio et al (2008)		609	75%	
Canada	Belletrutti et al (2007)	10 (1994–2003)	198	90%**	ICH 0%

ITP, immune thrombocytopenia; ICH, intracranial haemorrhage.

*61% treatment rates in 1995, 38% treatment in 2003.

**Lower treatment rates in the period 1999–2003.

Table III. Does treatment of newly diagnosed ITP change outcome? The Nordic immune thrombocytopenia (ITP) group divided centres into those that treat ITP versus those that do not; measurement of outcome in 6 months (Treutiger et al, 2007).

	More than two-thirds treated, %	One- to two-thirds treated, %	Less than one-third treated, %
Initial treatment rates	89	57	14
Day 15 platelet count > 20 × 10^9/l	67	67	52
Day 15 platelet count > 150 × 10^9/l	38	29	29
Chronic ITP	27	22	25
Disease-related events in 6 months	23	22	19

treated less than a third, between one- and two-thirds or greater than two-thirds of children with ITP. Results are shown in Table III. Overall, there was little difference between patients in the outcome measures assessed (Treutiger et al, 2007).

A summary of findings of the UK paediatric ITP registry shows a decreasing number of children are being treated over time. Only 16% of children were treated in 2011 compared to 61% in 1995. With the fall in treatment rates, there has been no reported impact on the incidence of ICH (Grainger et al, 2012).

Overall, treatment recommendations revolve around the prevention of ICH, without knowledge of what constitutes a risk of ICH.

Which patients are at risk of life-threatening bleeding and need to be treated emergently?

Low rates of bleeding

One of the striking features of paediatric ITP is the low rate of bleeding, even with platelet counts persistently $< 10 \times 10^9$/l. The Intercontinental Childhood ITP Study Group (ICIS) reported data from a prospective registry of haemorrhage at diagnosis, describing 25 of 863 children (2·9%) as developing severe haemorrhage (epistaxis, melena, menorrhagia and/or ICH) (Neunert et al, 2008). During the next 28 d, 3 of 505 (0·6%) of those with counts $< 20 \times 10^9$/l had new severe haemorrhagic events, irrespective of initial treatment (Neunert et al, 2008). Analysis of ICIS registry II participants describes data on 1345 subjects with no reports of ICH. Reporting of bleeding sites was variable, between 2% and 54% with no clear association with platelet count or duration of ITP. Although few patients were treated if no bleeding sites were reported, between 61% and 94% of patients were treated if 1 or more bleeding sites were recorded (Neunert et al, 2013).

Risks of ICH and morbidity

ICH remains uncommon, with between 0·1 and 3% reported in the small number of studies addressing this area (Tables II, IV). Given the limitations in collecting data, which relies on accurate reporting, these are only estimates. This could be an over-representation if patients with mild disease are not recorded, or an under-representation if all cases of ICH are not captured. In a review of cases of children who developed ICH in the USA, mucosal bleeding, including haematuria, was more common amongst children who developed ICH compared to those who did not. However, these features were not always present, and, although more common at lower platelet counts, patients had a wide range of counts at the time of presentation. The timing of ICH appears variable and was not restricted to acute or chronic ITP (Psaila et al, 2009). Mortality from ICH appears lower in later series; 57% in 1994 (Lilleyman, 1994), compared to 20–25% in later series. Head trauma, vascular anomalies, use of nonsteroidal anti-inflammatory drugs and association with lupus are other factors influencing the morbidity and mortality with ICH.

Overall, ICH appears to be rare, providing support for the no treatment approach, but with the caveat that patients with significant mucosal bleeding should be urgently treated.

The consensus document (Provan et al, 2010) includes a table outlining a bleeding/quality of life score ranging from 1, with minor bleeding and few petichiae, to grade 4, with mucosal bleeding or suspected internal haemorrhage. It is recommended that if patients only have cutaneous symptoms or less (grade 1 or 2), treatment may not be required; intervention is recommended with grade 3 (mucosal bleeding and troublesome lifestyle) and grade 4 (life-threatening bleed) symptoms (Provan et al, 2010).

This pathway has been developed with physicians of considerable experience, but has not been prospectively assessed for its ease of use in the general clinical setting, or in patient outcome if this pathway is followed. Furthermore the assessment of whether cutaneous symptoms require treatment leaves a grey area for interpretation.

Table IV. Summary of reviews of intracranial haemorrhage in children with ITP.

Reference, country	Patients (n)	ICH	Mortality	Platelet count at time of ICH ($\times 10^9$/l)	Additional factors
So et al (2013) Hong Kong	276	8 (3%)	1 (12%)	<10 in 50% 5–82	Acute (n = 3) Chronic (n = 5) Head trauma (n = 2) AVM (n = 1)
Choudhary et al (2009) India	750	17 (2%)	4 (24%)	2–50	Trauma (n = 1) (?NSAID) ICH at presentation (n = 5)
Psaila et al (2009) USA		40 (approx. 0·19–0·78%)	25%	<20 in 90% <10 in 75% 1–61	Head trauma (n = 13) NSAID (n = 3) Urinary bleed (n = 9)
Iyori et al (2000) Japan	772	4 (0·52%)	0	Median 5·2 ± 3·7	Menstruation (n = 2) Viral infections (n = 3) SLE (n = 3)
Lilleyman (1994) UK		14 (approx. 0·1%)	8 (57%)	<10–15	AVN (n = 2) Head injury (n = 2)
Elalfy et al (2010) Egypt	1840	10 (0·5%)	2 (20%)	<10 in 70%	Head trauma (n = 1) Acute ITP (n = 4) Persistent (n = 2) Chronic (n = 4)

ITP, immune thrombocytopenia; ICH, intracranial haemorrhage; AVM, arteriovenous malformation; NSAID, nonsteroidal anti-inflammatory drugs; SLE, systemic lupus erythematosus; AVN, avascular necrosis.

Given the association with head trauma and ICH, not treating also requires standardization regarding the life style changes that may be required. For example, whether children can participate in sports and, if so, which sports.

Can we extrapolate from acute, transient ITP: are there any consequences for many months or years of thrombocytopenia beyond ICH?

Treating fewer children with ITP has had little impact on ICH. However, for those who do not go into an immediate remission, there may be other effects of persistent thrombocytopenia. Platelets have other important roles, such as cytokine release and interaction with both the immune system and the endothelial system (Semple et al, 2011; Cloutier et al, 2012). There is little other data to enable the evaluation other effects of treating or not treating children with ITP, such as small internal haemorrhages with no overt clinical effect or subtle changes in the immune system. Furthermore, although changes in lifestyle for a short period of time may have little impact, for those with more prolonged thrombocytopenia, both the anxiety of the low platelet count and the avoidance of more risky activities such as skiing or rugby may have other effects on child development.

Health-related quality of life

Specifically designed to assess the impact on both children and parents, the kids ITP tools (KIT) questionnaire (Klaassen et al, 2007) has been developed and incorporated into a number of studies.

An assessment of Health-related quality of life (HRQoL) and platelet counts showed that bleeding severity correlated with platelet counts in children with chronic ITP but not in children with acute ITP. Platelet count and bleeding severity did not have a significant correlation with the KIT score (Neunert et al, 2009). The same group assessed 127 families (81 children) in four countries; KIT scores were lower in children with newly diagnosed ITP compared to chronic ITP (67·3 vs. 77·3; $P = 0·005$) and the child-reported scores correlated with the parent-proxy KIT scores (Klaassen et al, 2013). Although the children's scores increased in chronic disease, the parents' proxy scores (parents interpretation of the effects of the illness on the child) did not, indicating that the parents had a slower adaptation to ITP than the children. Assessment of 22 children with ITP treated on a randomized controlled study of romiplostim (17 receiving romiplostim and five placebo) showed no change in HRQoL for children treated with romiplostim compared to placebo (5 ± 10 vs. 7 ± 17 $P = 0·29$) (Klaassen et al, 2012). However, amongst parents, there was a significant improvement in the romiplostim treated arm (24 ± 17 vs. 6 ± 8 $P = 0·008$), again reflecting a difference between the child and the parent view of ITP (Klaassen et al, 2012).

In a separate group from Israel, the KIT questionnaire was administered to 17 children with ITP and their parents ($n = 34$) attending a tertiary pediatric medical centre. The mean KIT score was lower in the parents' group [4·04 standard deviation (SD) 0·7] when compared to the children's group 2·99 (SD 0·7). Children were mostly concerned about restriction on physical activities, whereas parents were concerned about disease side effects and their child's future. The presence of acute versus chronic disease had no impact on the KIT score in either group. There was also no difference in scores between patients receiving active treatment (3·07 SD 0·45) compared to those in remission (2·8 SD 0·88) (Zilber et al, 2012).

In the UK, a questionnaire-based survey to identify health-related lifestyle concerns among adults and children with primary ITP was performed (Sarpatwari et al, 2010a). A 43-question, closed-field questionnaire addressing bruising and bruising frequency, disease management, social engagement, work and school performance and recreational activities was mailed to 1767 members of the ITP support organization. 94 children (or families) responded. Bruising occurred in 56·8% of children. Children were more likely than adults to experience frustration over activity restrictions (23·3% vs. 9·5% respectively; $P < 0·001$). The impact of primary ITP on healthcare, insurance coverage and social engagement was more pronounced among adults. However, 12·5% of all patients with primary ITP (adults and children) reported 'always' or 'often' missing work or school due to fatigue. These absences were not significantly associated with disease severity ($P = 0·301$) (Sarpatwari et al, 2010a).

Fatigue

Patients and parents frequently report increased fatigue and irritability when platelet counts are low. In a retrospective analysis of the notes of 27 children with ITP, fatigue was reported in six children (22%). Fatigue did not appear to be related to treatments, to other medical problems or occurrence of anaemia. Although only a retrospective analysis of notes, this is a reasonable percentage of patients, which may be higher if properly evaluated (Blatt et al, 2010). Fatigue may relate to the immune disease, or to contributing activities of the platelets. Preliminary cognitive assessments also show changes in patients with ITP (Frith et al, 2012). These studies need further evaluation.

While over treatment is unnecessary, restricting children in both physical and mental activities due to fatigue also needs to be considered when managing patients. This is reflected in the guidelines, which suggest patients should be evaluated for how they are coping psychologically with the low platelet count (Provan et al, 2010; Neunert et al, 2011).

By not treating, will we increase the rate of chronic ITP?

Data from 1984 children entered in registry 1 of the ICIS showed a difference in the 6-month outcome of children with ITP depending on the treatment given (Tamminga et al,

2009). A matched pairs analysis compared children with thrombocytopenia (platelet count $< 150 \times 10^9$/l) 6 months after diagnosis with those with normal platelet counts at 6 months. Patients who were initially treated with intravenous immunoglobulin (IVIG) were more likely to have a normal platelet count at 6 months, independent of age, gender, country of origin, platelet count at diagnosis or infection preceding diagnosis. In the patients with a platelet count $< 50 \times 10^9$/l 6 months after diagnosis, they were less often treated with IVIG than with steroids (Tamminga et al, 2009). Although statistically significant, the numerical difference between the groups was small. However, this warrants further exploration of the cause of ITP, and whether different treatments or no treatment may influence the course of the disease.

Areas that require more research include: whether any of the impact of IVIG relates to increased clearance of infection or antibody load, and whether not treating results in persistent destruction of platelets influencing disease progression.

Treating ITP

Seventy to 80% of children diagnosed with ITP will go into a complete remission within a few months of the episode, with or without treatment. If the thrombocytopenia persists, re-assessing the diagnosis is paramount.

Is it ITP?

ITP remains a diagnosis of exclusion, with no specific tests. Careful history-taking and evaluation with other diagnostic tests are vital for diagnosis and appropriate management. A retrospective chart review over a 10-year period showed that 14% of 492 children were eventually diagnosed with another disorder: the most common (but not exclusive to) included familial thrombocytopenia, systemic lupus erythematosis, hyperspenism, neonatal alloimmune thrombocytopenia, Wiskott-Aldrich syndrome or systemic infection (Bryant & Watts, 2011). Other important associations include common variable immunodeficiency, encompassing IgA deficiency and cytomegalovirus (CMV), causing or complicating ITP (DiMaggio et al, 2009).

Secondary ITP is often more difficult to manage and involves specifically tailored treatment. For example, treatment of the underlying disease, such as viruses, lupus or immunodeficiency; adapting the choice of treatment, such as immunosuppression and avoidance of splenectomy for those with other autoimmune diseases or avoidance of immunosuppression with other immunodeficiency disorders or in those with hepatitis C, CMV or HIV.

Bone marrow assessments

Whether a bone marrow examination is required is also controversial. Retrospective studies spanning the last 20 years suggest a very low incidence of other diagnoses on marrow findings in patients with typical ITP findings, generally advocating that bone marrows are not needed unless atypical features are identified (Jones & Boyko, 1985; Halperin & Doyle, 1988; Dubansky et al, 1989; Calpin et al, 1998; Jubelirer & Harpold, 2002). Not going into an early remission, or lack of response to standard treatment is atypical for paediatric ITP. If second line treatments, such as rituximab, immunosuppression, splenectomy or thrombopoietin receptor agonists (TPO-RAs), are to be used, bone marrow aspirate and trephine biopsies are recommended (Geddis & Balduini, 2007). Although the detection of other abnormalities may be unlikely, one reason for performing bone marrow biopsies is to establish that the bone marrow is normal before treatments with known and unknown potential complications (such as TPO-RAs).

H. Pylori assessment and eradication

The prevalence or Helicobacter pylori (H. pylori) in patients with ITP and the response rates of ITP to its treatment in both adults and children appear to vary widely, and have interesting country-related differences. For example, in a large study reported in Italy, 13/33 (39%) children who had successful H. pylori eradication therapy had a platelet response compared to spontaneous remission in 17/166 (10%) – amongst children with chronic ITP (Russo et al, 2011). Studies from Italy and Japan appear to demonstrate the highest response rates in adults with ITP and H. pylori. The 2011 American Society of Hematology (ASH) guidelines (Neunert et al, 2011) do not recommend investigating for H. pylori, due to lack of evidence base. However, diagnosing and treating H. pylori is easy, has few adverse effects (if any) and, if responsive, may allow children to avoid other prolonged therapy. Further analysis is warranted.

Treatment: newly diagnosed, or acute fall in platelet count

Treatment is aimed at treating bleeding, or reducing the risk of serious bleeding without engendering treatment-related risks. An important part of the no-treatment approach is to recognize the urgency of managing bleeding in those who do require treatment, which may require multiple treatment modalities.

Standard first line therapy in all the guidelines and consensus documents remains steroids (George et al, 1996; British Committee for Standards in Haematology General Haematology Task Force, 2003; Provan et al, 2010; Neunert et al, 2011). However, there is not consensus on this dosing schedule. Short courses of high dose prednisolone, such as 3–4 mg/kg, are recommended by some groups, and can rapidly increase the count, potentially avoiding prolonged courses of steroids, although the long-term data remains limited (Carcao et al, 1998). There are few published comparisons of

low dose *versus* high dose, particularly the very short high dose regimen. Side effects of steroids are the main burden of disease in patients with ITP. Whether short courses of high dose or longer courses of lower doses have different effects on events such as bone mineralization or mood changes has not been evaluated. The maximum recommended dose of steroids has also not been established.

In those in whom steroids are contra-indicated or in whom the diagnosis is not clear, IVIG can be used at 0·8 g/kg. This regime can be added to steroids if the child is considered to be at high risk of bleeding. If the platelet count has not increased and the child remains at risk of bleeding, a second dose of IVIG can be given. Side effects of IVIG can also be problematic. Use of pre-medication including paracetamol, antihistamines and steroids is very important, and changing products in this circumstance may be helpful.

Anti-D in place of IVIG has previously been recommended as first line therapy. However, rare cases of intravascular haemolysis (IVH), associated with renal failure and mortality has been reported (Despotovic *et al*, 2012). Due to this incidence of IVH, a black box warning has been added, and the license has been withdrawn from the European market. In the USA, it is now recommended only for patients with severe ITP refractory to other treatments. Exclusion criteria include: patients with leukaemia, lymphoma, Epstein-Barr virus or hepatitis C infections, those older than 65 years, those with conditions which make them more likely to develop haemolysis (Evan syndrome, systemic lupus erythematosus, autoimmune lymphoproliferative syndrome). In addition, it is recommended that patients stay under observation for 8 h, which abrogates some of the advantages of Anti-D (i.e. its short infusion time).

Although platelet transfusions are not recommended in ITP, in the context of ICH or other severe bleeding, the addition of platelet transfusions may be required whilst waiting for the effects of treatment. In life-threatening situations, multiple modes of therapy may be required simultaneously.

Tranexamic acid

Tranexamic acid can be very useful in patients with thrombocytopenia. It is used frequently in patients with menorrhagia. However, there is little published evidence for its use in children beyond case reports and reviews.

Recombinant activated factor VII (rFVIIa)

Increasingly there are reports of the use of rFVIIa in patients with ITP and bleeding. It has been used in both children and in adults, mostly published as case reports (Salama *et al*, 2009). There are no clinical trials in this area and the majority of patients were on many different agents, making the interpretation of the responses difficult. *In vitro* data also shows a synergistic effect of rfVIIa and fibrinogen on whole blood clot formation correcting the coagulopathy of ITP, even at very low platelet counts. The authors of this study suggest it may be a useful alternative to platelet transfusion and recommend clinical trials (Larsen *et al*, 2013). As with most treatments of ITP, this remains an unlicensed indication requiring further evaluation.

Treatment: chronic

Chronic ITP in children remains rare and also not consistently defined. The standardization document, compiled from discussion amongst 20 treating clinicians, elected to describe children and adults as having chronic ITP if the thrombocytopenia persists for more than 12 months (Rodeghiero *et al*, 2009). One of the aims of the document was to provide a more consistent definition and to improve future analysis.

Management of children who do not go in to an early remission is debatable and can be polemic. This reflects the rarity of the disease and the absence of high-grade evidence. In addition to discussions on which patients require treatment, which treatment should be used also has little evidence base. Controversies include, whether to, and in whom to, consider splenectomy; how safe is rituximab, what dose to use and how frequently can it be used? Immunosuppression, such as azathioprine and mycophenolate (MMF), although widely used in other paediatric diseases, feature little in the management of children with ITP. Finally, TPO-RAs show great promise due to their high efficacy and low toxicity but long-term safety data is not yet available in children.

Splenectomy

Splenectomy remains the only treatment that appears to have a long lasting effect in patients with ITP. In children with chronic ITP, response rates are around 70% (Table V). Most series describe low adverse events with no associated mortality in the cases reported in Table V. Post-splenectomy sepsis was frequently reported, with seven of 132 patients in one report, although there were no fatalities (Kühne *et al*, 2007). Laparoscopic splenectomy has fewer overall complications. However, the long-term consequences of splenectomy are not well known.

The four guidelines show considerable differences in recommendations for splenectomy (George *et al*, 1996; British Committee for Standards in Haematology General Haematology Task Force, 2003; Provan *et al*, 2010; Neunert *et al*, 2011; discussed further in Breakey & Blanchette, 2011). The more recent ASH guidelines (Neunert *et al*, 2011) recommend delaying surgery to after 12 months, whereas the consensus document (Provan *et al*, 2010) suggest that splenectomy is rarely necessary.

As with all therapies for ITP, the potential adverse events of splenectomy need to be considered along side the long-term

Table V. Summary of splenectomy responses.

Reference	Number patients splenectomized	Complete response (%)
George et al (1996)	271	72
Blanchette et al (1992)	21	81
Ben-Yehuda et al (1994)	27	67
Mantadakis and Buchanan (2000)	38	76
Kühne et al (2007)	132	69
Overall	488	71·5

side effects of other therapies, and the long-term effects of persistent thrombocytopenia. Reported cases of pulmonary hypertension and increased thromboembolic events post-splenectomy may relate to the underlying disease. More recently, a cohort analysis of 9976 adults with ITP, 1762 of whom underwent splenectomy, described an increased risk of abdominal venous thromboembolism early after splenectomy [hazard ratio (HR) 5·4 confidence interval (CI) 2·3–12·5] and venous thrombus (deep venous thrombosis and pulmonary embolus) both early [HR 5·2 (CI 3·2–8·5)] and late [HR 2·7 (CI 1·9–3·8)] after splenectomy compared to those who had not undergone splenectomy (Boyle et al, 2013). In addition, there was a higher adjusted risk of sepsis both early [HR 3·3 (CI 2·4–4·6)] and late (HR 1·6 or 3·1 depending on co-morbidities) post-splenectomy. However, in the adjusted model, splenectomy was associated with a significant reduction in the odds of death (Boyle et al, 2013). Whether this has any relevance in a paediatric setting, where thrombotic events are far less frequent, is not clear.

In a summary of post-splenectomy complications in adults with ITP versus indication-matched controls (Rodeghiero & Ruggeri, 2012) infection was increased 2·6-fold for first 90 d, but not thereafter (Thomsen et al, 2009), venous thromboembolism increased approximately 2-fold versus appendectomy, (Thomsen et al, 2010), mortality increased 2·3-fold for the first 90 d and thereafter [relative risk (RR) 0·4] (Young et al, 2010). Overall, although 30–40% do not go into a long-term remission, only about 10% remain refractory and complications are apparent in <1%.

Many patients are also reluctant to undergo surgery, particularly without a guarantee of outcome. Splenic destruction scans may help to better define this (Cuker & Cines, 2010; Sarpatwari et al, 2010b).

The benefits for those who respond to splenectomy and do not have further episodes of thrombocytopenia requiring intervention needs to be balanced against the small risks of adverse events in patients undergoing splenectomy. Understanding of the biology of ITP and biomarkers of which patients are unlikely to acheive a long-term remission are also required to help aid decision-making.

Rituximab

Rituximab therapy has the benefit of long duration of response (6–12 months). It can be used as a steroid-sparing agent early on in disease and can allow children to have many months 'free of disease'. However, very few patients (children or adults) achieve long-term remissions with rituximab (Patel et al, 2012). We previously reported a review of responses to rituximab in children with ITP, showing similar responses to that of adults, with a good safety profile (Cooper & Bussel, 2010). A systematic review published earlier this year confirmed these results, with 39% complete remissions and 68% partial remissions from 14 studies with a total of 323 patients (Liang et al, 2012). Median response duration was 12·8 months. Most adverse events were mild to moderate, with no deaths reported (Liang et al, 2012).

Adverse events are rare with rituximab, but can be serious. Progressive multifocal leucoencephalopathy, although almost exclusively reported after bone marrow transplantation, in the context of lupus, or following multiple chemotherapy, has been reported in adults with ITP (Carson et al, 2009). Hypogammaglobulinaemia has also been reported amongst adults and children (Cooper et al, 2009), although the overall number is unclear, and appears to occur with repeated doses and in patients with underlying immune dysfunction. Studies have shown impaired humoral responses to vaccination after rituximab (Yri et al, 2011). This may represent subtle changes in immune responses to infections. If possible, children should be vaccinated before treatment. This is particularly relevant if splenectomy is to be considered in the future.

Overall, although one course may be useful, most patients will relapse, and repeated doses of rituximab in young children should be used with caution, unless long-term safety data can clarify its safety. In the absence of further clinical trials, children receiving rituximab should be recorded on national or international registries, and long-term outcome and safety should be assessed, including the effects on B cell repopulation and immunoglobulin levels and infectious complications.

Immunosuppression

The consensus document and the ASH guidelines (Provan et al, 2010; Neunert et al, 2011) do not recommend the use of these agents in children with ITP, due to lack of evidence. However immunosuppression, such as azathioprine and MMF are used extensively in other autoimmune conditions in children with good safety prolife. This is an area that needs further evaluation with prospective studies.

Thrombopoietic agonists

TPO-RAs are novel agents that are specifically designed to increase the platelet count. Two agents are currently licensed

for use in adults with chronic refractory ITP who are refractory to, or who have a contraindication to splenectomy [both have been approved by the National Institute for Health and Care Excellence (NICE)], with a number of other agents in pipeline development. Both agents work through the thrombopoietin receptor although with different modes of activation.

Romiplostim (AMG 53, Nplate; Amgen, Thousand Oaks, CA) is a recombinant protein classified as a peptibody. It is comprised of an IgG Fc domain linked to four identical recombinant peptides. The Fc piece of the molecule causes it to be recycled via the neonatal Fc receptor (FcRn), extending its half-life. It activates through the thrombopoietin binding site. It is given as a subcutaneous injection once a week.

In placebo-controlled studies in adults, romiplostim showed greater response rates (less treatment failures) and reduction in rescue medications in treatment compared to non-treatment arms, in both splenectomized and non-splenectomized patients (Bussel et al, 2009; Kuter et al, 2010). In a long-term extension study, 87% of patients had a platelet response, with 78% of patients maintaining counts of more than 50×10^9/l for more than 10 weeks (Bussel et al, 2009). The 5-year outcome study, with over 614 patient-years of exposure, showed no new adverse events; thrombotic events occurred in 6·5% of patients, not associated with platelet count; platelet responses were maintained in 92% of study visits (Kuter et al, 2013).

In children, two studies are currently reported. The largest describes 15/17 children (88%) with a response to romiplostim (platelet count $\geq 50 \times 10^9$/l) compared to none of the five patients randomized to placebo. The median weekly dose was higher in children (5 µg/kg). There were no treatment-related serious adverse events. The most commonly reported adverse events in children, as in adults, were headache and epistaxis (Bussel et al, 2011). In a second study, 10/12 (83·3%) responded to romiplostim, again with no serious adverse events (Elalfy et al, 2011).

Eltrombopag (SB-497115; GSK, Brentford, UK) is an oral agent taken once a day. It is a small molecule, a non-peptide, which activates the thrombopoietin receptor at the transmembrane domain, and not at the thrombopoietin receptor site.

In a randomized controlled study comparing eltrombopag to placebo [Randomized Placebo-Controlled ITP Study With Eltrombopag (RAISE)], adults receiving eltrombopag had greater odds of achieving the primary outcome of a platelet count between 50 x 10 /l and 400 x 10 /l during the 6-month treatment period than placebo [odds ratio (OR) 8·2, 99% CI 3·6, 18·7]. In patients receiving eltrombopag, 50/83 (60%) of non-splenectomized patients and 18/49 (37%) of splenectomized patients achieved platelet counts > 50×10^9/l. Adults receiving eltrombopag required less rescue medication and had lower odds of bleeding events (Cheng et al, 2011). Long-term extension studies show continued safety and efficacy (Saleh et al, 2013).

Studies of the use of eltrombopag in children are ongoing and expected to be reported later this year.

The safety and tolerability in adults for both agents has been good, with no difference between placebo and treatment arms.

Real and potential adverse events (reported in adults) (reviewed in Cuker, 2010):

1 Thromboembolic events appeared higher than expected (approximately 5%) in both studies (Kuter et al, 2013; Saleh et al, 2013), although the difference between placebo and treatment arms was not significant, suggesting the thrombotic risk may relate to ITP itself.
2 Bone marrow changes, with increased reticulin deposition and features similar to myeloproliferative disorders have been reported (Boiocchi et al, 2012; Ghanima et al, 2014). This appears to be reversible on stopping treatment. Ongoing studies are investigating the cause and degree of this adverse event.
3 Increased liver function tests in patients treated with eltrombopag. This also appears reversible and no patient has gone on to develop irreversible liver disease (Maddrey et al, 2009).
4 Rebound thrombocytopenia occurs if the agents are stopped abruptly (Bussel et al, 2006; Cheng et al, 2009).
5 Fluctuating platelet counts occur in some patients and can be difficult to manage. There may be a difference between agents, although this has not been formally assessed. The diagnosis of ITP should be re-evaluated in these circumstances.
6 Potential for stem cell stimulation. At the time of publication, no adverse events have been documented on the stem cell proliferation effects of TPO-RAs.

As with the introduction of all growth factors, there is the theoretical concern over long-term stimulation of stem cells. To date, there are no publications of concern in this area, although the experience in children remains limited and requires ongoing vigilance and studies of the effects on the bone marrow.

A small number of adults treated with both romiplostim and eltrombopag have been able to come off treatment after a period of time, even those with severe refractory disease. This could be related to the ability of TPO-RA to correct platelet production defects or induction of immune tolerance and needs to be further explored.

Until more long-term safety data is available, these agents should be used within the context of a clinical trial. If trials are not available, patients should only be initiated and managed in conjunction with specialists with experience in using TPO-RA. Long-term follow up of patients should be captured by national registry databases.

Summary/Discussion

In children who have acute ITP, with a self-limiting period of thrombocytopenia and with no or little bleeding, the UK registry data has shown that ascribing no treatment has not

resulted in any immediate increase in ICH. The risks of bleeding remain low and the adverse effects of steroids or immunoglobulins may have a greater risk.

However, a small number of patients do suffer from bleeding and require treatment. Not treating relies on avoidance of

risks, and an understanding of when intervention is required, such as head injury and degree of bleeding. Also, for those who have a prolonged period of thrombocytopenia, the risks and adverse effects of no treatment have not been fully explored. Some patients, both children and adults experience

Table VI. Which children need to be treated? Establishing the risks of thrombocytopenia.

Questions	Potential methods of analysis
Which patients are at risk of life-threatening bleeding?	Registry data and retrospective analysis of ICH cases: establishing risk factors Establish an international registry for patients who develop ICH
Can we predict which patients presenting acutely will develop long-term thrombocytopenia?	Registry data in association with biomarkers taken at diagnosis and correlated with long-term outcome
What impact does ITP have on emotional and cognitive development?	Prospective HRQoL and cognitive assessment of all children presenting with ITP
Is the presence of bruises or petechia associated with other adverse effects?	Correlation of bleeding scores with long-term outcome Novel assessments of internal bleeding
Is the platelet count predictive of adverse outcome?	Correlation of the platelet count with bleeding scores, occurrence of ICH, and long-term outcome including cognitive and HRQoL assessments
Does treatment alter outcome?	Randomized controlled studies of treatment *versus* no treatment in low or intermediate risk patients: evaluation of the effects on long-term remission

ITP, immune thrombocytopenia; ICH, intracranial haemorrhage; HRQoL, health-related quality of life.

Table VII. Evaluating treatments in childhood ITP.

Questions	Potential methods for resolution
Should high-dose steroids, low-dose steroids or IVIG be used in acute bleeding or prior to procedures?	Randomized controlled studies of low dose *versus* high dose steroids *versus* IVIG in children requiring treatment Assessment of short and long term responses, assessment of bleeding, cognitive and HRQoL studies and assessments of adverse effects (including bone metabolism)
How safe and effective are immunosuppressives, such as MMF and azathioprine?	Retrospective safety and efficacy from registry data Prospective studies of safety and efficacy

Should anti-CD20 agents, TPO-RAs, or splenectomy be used in patients with prolonged thrombocytopenia, requiring treatment?	1. All patients on TPO-RAs and anti-CD20 agents such as rituximab should be entered onto long-term registries
	
	Analysis of outcome including CR, PR and duration of response
	Anti-CD20:
	  i. How many children relapse following anti-CD20, requiring further treatment?
	  ii. What is the long-term safety of anti-CD20 agents? Ig levels, incidence of PML, and incidence of infections to be recorded
	TPO-RAs:
	  i. How many patients go into remission on a short course of TPO-RAs?
	  ii. Analysis of adverse effects from TPO-RAs, including prospective assessment of bone marrow effects
	
	2. Randomized study of anti-CD20 agent *versus* TPO-RAs (±MMF)
	3. How do these agents compare to long-term splenectomy follow-up data?
	Outcome data should include: CR, PR, long-term responses, adverse events (including treatment-specific effects, such as bone marrow analysis, in prospective studies of TPO-RAs, IgGs and infections after rituximab) and psychological and social impact

ITP, immune thrombocytopenia; IVIG, intravenous immunoglobulin; MMF, mycophenolate; HRQoL, health-related quality of life; TPO-RA, Thrombopoietin receptor agonist; CR, complete response; PR, partial response; Ig(G), immunoglobulin (G); PML, progressive multifocal leucoencephalopathy.

fatigue and quality of life limitations when platelets are low. Furthermore, not treating children with ITP can render anxiety around what constitutes a risk, which causes change in parental and child behavior. This may have more long-term impact on child health. Management aims, in addition to avoiding bleeds and minimizing treatment side effects, should also encompass maintaining a 'normal' quality of life.

Although long- or medium-term steroids have adverse effects and should be avoided, other agents, such as azathioprine or MMF have few immediate side effects and require further evaluation in this area. Rituximab, at least for a single course does, not appear to have significant toxicity, even on an immature immune system, however, subtle changes in the immune system make this a less attractive option, and repeated doses should be used with caution; immunoglobulin levels and responses to vaccination should be assessed. Splenectomy is controversial, but still has a place in the management of certain children with ITP, especially until the long-term safety of other agents have been evaluated and compared. TPO-RAs have changed the management of adults with ITP. So far, their safety profile has been impressive. Long-term safety evaluations are needed, especially of their effects on a young bone marrow. If further clinical trials are not funded, children commenced on novel agents should be managed within a specialized centre, and carefully followed in national registries. Regulatory bodies and pharmaceutical companies should be encouraged to ensure this data is accurately collected. The impact of these agents on an immature bone marrow should be formally assessed.

Finally, there is very little evidence base on which to make clinical decisions. This is reflected in all of the reviews and consensus documents, with difficulties in advising either on who should be treated or on which second line therapies should be prescribed. Long-term follow up of patients, using the national and international registries are helping to establish these effects. In the UK, the ITP patient support group and the UK ITP forum is aimed at improving communication and with it, patient care. Through these mediums, a more rigorous assessment of the risks of low platelet count should be performed. Well-designed studies are needed to properly evaluate the effects of treating *versus* not treating both in terms of internal bleeding, cognitive effects and HRQoL effects. Comparison of the efficacy, and the side effects of treatments including rituximab, MMF and TPO-RAs are needed. Although splenectomy remains an important intervention, the comparison of a surgical procedure with medical procedure remains problematic. However, long-term studies of the adverse effects of splenectomy and of the long-term responses are published and could be compared.

A summary of the questions still to be resolved, and potential methods of analysis are suggested in Tables VI and VII. Although ambitious and covering many aspects of care, discussion through international groups may help to resolve these issues.

ITP is a diverse disease and its optimal management requires balancing therapeutic risk. While many children can be left untreated, they continue to represent significant management challenge.

Conflicts of interest

References

Belletrutti, M., Ali, K., Barnard, D., Blanchette, V., Chan, A., David, M., Luke, B., Price, V., Ritchie, B. & Wu, J.; Canadian Pediatric Chronic ITP Working Group; Canadian Pediatric Thrombosis and Hemostasis Network. (2007) Chronic immune thrombocytopenic purpura in children: a survey of the Canadian experience. *Journal of Pediatric Hematology and Oncology*, **29**, 95–100.

Ben-Yehuda, D., Gillis, S. & Eldor, A.; Israeli ITP Study Group. (1994) Clinical and therapeutic experience in 712 Israeli patients with idiopathic thrombocytopenic purpura. *Acta Haematologica*, **91**, 1–6.

Blanchette, V.S., Kirby, M.A. & Turner, C. (1992) Role of intravenous immunoglobulin G in autoimmune hematologic disorders. *Seminars in Hematology*, **29**(3 Suppl. 2), 72–82.

Blatt, J., Weston, B. & Gold, S. (2010) Fatigue as marker of thrombocytopenia in childhood idiopathic thrombocytopenic purpura. *Pediatric Hematology and Oncology*, **27**, 65–67.

Boiocchi, L., Orazi, A., Ghanima, W., Arabadjief, M., Bussel, J.B. & Geyer, J.T. (2012) Thrombopoietin receptor agonist therapy in primary immune thrombocytopenia is associated with bone marrow hypercellularity and mild reticulin fibrosis but not other stromal abnormalities. *Modern Pathology*, **25**, 65–74.

Boyle, S., White, R.H., Brunson, A. & Wun, T. (2013) Splenectomy and the incidence of venous thromboembolism and sepsis in patients with immune thrombocytopenia. *Blood*, **121**, 4782–4790.

Breakey, V.R. & Blanchette, V.S. (2011) Childhood immune thrombocytopenia: a changing therapeutic landscape. *Seminars in Thrombosis and Hemostasis*, **37**, 745–755.

British Committee for Standards in Haematology General Haematology Task Force. (2003) Guidelines for the investigation and management of idiopathic thrombocytopenic purpura in adults, children and in pregnancy. *British Journal of Haematology*, **120**, 574–596.

Bryant, N. & Watts, R. (2011) Thrombocytopenic syndromes masquerading as childhood immune thrombocytopenic purpura. *Clinical Pediatrics*, **50**, 225–230.

Bussel, J.B., Kuter, D.J., George, J.N., McMillan, R., Aledort, L.M., Conklin, G.T., Lichtin, A.E., Lyons, R.M., Nieva, J., Wasser, J.S., Wiznitzer, I., Kelly, R., Chen, C.F. & Nichol, J.L. (2006) AMG 531, a thrombopoiesis-stimulating protein, for chronic ITP. *New England Journal of Medicine*, **355**, 1672–1681.

Bussel, J.B., Kuter, D.J., Pullarkat, V., Lyons, R.M., Guo, M. & Nichol, J.L. (2009) Safety and efficacy of long-term treatment with romiplostim in thrombocytopenic patients with chronic ITP. *Blood*, **113**, 2161–2171.

Bussel, J.B., Buchanan, G.R., Nugent, D.J., Gnarra, D.J., Bomgaars, L.R., Blanchette, V.S., Wang, Y.M., Nie, K. & Jun, S. (2011) A randomized, double-blind study of romiplostim to determine its safety and efficacy in children with immune thrombocytopenia. *Blood*, **118**, 28–36.

Calpin, C., Dick, P., Poon, A. & Feldman, W. (1998) Is bone marrow aspiration needed in acute childhood idiopathic thrombocytopenic purpura to rule out leukemia? *Archives of Pediatric Adolescent Medicine*, **152**, 345–347.

Carcao, M.D., Zipursky, A., Butchart, S., Leaker, M. & Blanchette, V.S. (1998) Short-course oral prednisone therapy in children presenting with acute immune thrombocytopenic purpura (ITP). *Acta Paediatric Supplement*, **424**, 71–74.

Carson, K.R., Evens, A.M., Richey, E.A., Habermann, T.M., Focosi, D., Seymour, J.F., Laubach, J., Bawn, S.D., Gordon, L.I., Winter, J.N., Furman, R.R., Vose, J.M., Zelenetz, A.D., Mamtani, R., Raisch, D.W., Dorshimer, G.W., Rosen, S.T., Muro, K., Gottardi-Littell, N.R., Talley, R.L., Sartor, O., Green, D., Major, E.O. & Bennett, C.L. (2009) 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*, **113**, 4834–4840.

Cheng, G., Tarantino, M., Gernsheimer, T., Meyer, O., Brainsky, A. & Stone, N.L. (2009) Platelet counts following eltrombopag discontinuation in patients with chronic immune thrombocytopenic purpura. *Blood (ASH Annual Meeting Abstracts)*, **114**, 3517.

Cheng, G., Saleh, M.N., Marcher, C., Vasey, S., Mayer, B., Aivado, M., Arning, M., Stone, N.L. & Bussel, J.B. (2011) Eltrombopag for management of chronic immune thrombocytopenia (RAISE): a 6-month, randomised, phase 3 study. *Lancet*, **377**, 393–402.

Choudhary, D.R., Naithani, R., Mahapatra, M., Kumar, R., Mishra, P. & Saxena, R. (2009) Intracranial hemorrhage in childhood immune thrombocytopenic purpura. *Pediatric Blood Cancer*, **52**, 529–531.

Cloutier, N., Paré, A., Farndale, R.W., Schumacher, H.R., Nigrovic, P.A., Lacroix, S. & Boilard, E. (2012) Platelets can enhance vascular permeability. *Blood*, **120**, 1334–1343.

Cooper, N. & Bussel, J.B. (2010) The long-term impact of rituximab for childhood immune thrombocytopenia. *Current Rheumatology Reports*, **12**, 94–100.

Cooper, N., Davies, E.G. & Thrasher, A.J. (2009) Repeated courses of rituximab for autoimmune cytopenias may precipitate profound hypogammaglobulinaemia requiring replacement intravenous immunoglobulin. *British Journal of Haematology*, **146**, 120–122.

Cuker, A. (2010) Toxicities of the thrombopoietic growth factors. *Seminars in Hematology*, **47**, 289–298.

Cuker, A. & Cines, D.B. (2010) Evidence-based mini-review: is indium-labeled autologous platelet scanning predictive of response to splenectomy in patients with chronic immune thrombocytopenia? *Hematology American Society of Hematology Education Program*, **2010**, 385–386 Review.

Del Vecchio, G.C., De Santis, A., Giordano, P., Amendola, G., Baronci, C., Del Principe, D., Nobili, B., Jankovic, M., Ramenghi, U., Russo, G., Zecca, M. & De Mattia, D.; AIEOP ITP Study Group. (2008) Management of acute childhood idiopathic thrombocytopenic purpura according to AIEOP consensus guidelines: assessment of Italian experience. *Acta Haematologica*, **119**, 1–7.

Despotovic, J.M., Lambert, M.P., Herman, J.H., Gernsheimer, T.B., McCrae, K.R., Tarantino, M.D. & Bussel, J.B. (2012) RhIG for the treatment of immune thrombocytopenia: consensus and controversy (CME). *Transfusion*, **52**, 1126–1136.

DiMaggio, D., Anderson, A. & Bussel, J.B. (2009) Cytomegalovirus can make immune thrombocytopenic purpura refractory. *British Journal of Haematology*, **146**, 104–112.

Dubansky, A.S., Boyett, J.M., Falletta, J., Mahoney, D.H., Land, V.J., Pullen, J. & Buchanan, G. (1989) Isolated thrombocytopenia in children with acute lymphoblastic leukemia: a rare event in a Pediatric Oncology Group Study. *Pediatrics*, **84**, 1068–1071.

Elalfy, M., Elbarbary, N., Khaddah, N., Abdelwahab, M., El Rashidy, F., Hassab, H. & Al-Tonbary, Y. (2010) Intracranial hemorrhage in acute and chronic childhood immune thrombocytopenic purpura over a ten-year period: an Egyptian multicenter study. *Acta Haematologica*, **123**, 59–63.

Elalfy, M.S., Abdelmaksoud, A.A. & Eltonbary, K.Y. (2011) Romiplostim in children with chronic refractory ITP: randomized placebo controlled study. *Annals of Hematology*, **90**, 1341–1344.

Frith, J., Watson, S., Bolton Maggs, P.H.B. & Newton, J.L. (2012) Cognitive symptoms are common in immune thrombocytopenia and associate with autonomic symptom burden. *European Journal of Haematology*, **88**, 224–228.

Geddis, A. & Balduini, C.L. (2007) Diagnosis of immune thrombocytopenic purpura in children. *Current Opinion in Hematology*, **14**, 520–525.

George, J.N., Woolf, S.H., Raskob, G.E., Wasser, J.S., Aledort, L.M., Ballem, P.J., Blanchette, V.S., Bussel, J.B., Cines, D.B., Kelton, J.G., Lichtin, A.E., McMillan, R., Okerbloom, J.A., Regan, D.H. & Warrier, I. (1996) Idiopathic thrombocytopenic purpura: a practice guideline developed by explicit methods for the American Society of Hematology. *Blood*, **88**, 3–40.

Ghanima, W., Geyer, J.T., Lee, C.S., Boiocchi, L., Imahiyerobo, A.A., Orazi, A. & Bussel, J.B. (2014) Bone marrow fibrosis in 66 immune thrombocytopenia patients treated with thrombopoietin receptor agonists: a single center long-term follow-up. *Haematologica*, doi: 10.3324/haematol.2013.09892.

Grainger, J.D., Rees, J.L., Reeves, M. & Bolton-Maggs, P.H. (2012) Changing trends in the UK management of childhood ITP. *Archives of Disease in Childhood*, **97**, 8–11.

Halperin, D.S. & Doyle, J.J. (1988) Is bone marrow examination justified in idiopathic thrombocytopenic purpura? *American Journal of Diseases of Childood*, **142**, 508–511.

Iyori, H., Bessho, F., Ookawa, H., Konishi, S., Shirahata, A., Miyazaki, S., Fujisawa, K. & Akatsuka, J. (2000) Japanese Study Group on childhood ITP. Intracranial hemorrhage in children with immune thrombocytopenic purpura. Japanese Study Group on childhood ITP. *Annals of Hematology*, **79**, 691–695.

Jones, E.C. & Boyko, W.J. (1985) Diagnostic value of bone marrow examination in isolated thrombocytopenia. *American Journal of Clinical Pathology*, **84**, 665–667.

Jubelirer, S.J. & Harpold, R. (2002) The role of the bone marrow examination in the diagnosis of immune thrombocytopenic purpura: case series and literature review. *Clinical Applied Thrombosis and Hemostasis*, **8**, 73–76.

Kime, C., Klima, J., Rose, M.J. & O'Brien, S.H. (2013) Patterns of inpatient care for newly diagnosed immune thrombocytopenia in US children's hospitals. *Pediatrics*, **131**, 880–885.

Klaassen, R.J., Blanchette, V.S., Barnard, D., Wakefield, C.D., Curtis, C., Bradley, C.S., Neufeld, E.J., Buchanan, G.R., Silva, M.P., Chan, A.K. & Young, N.L. (2007) Validity, reliability, and responsiveness of a new measure of health-related quality of life in children with immune thrombocytopenic purpura: the Kids' ITP Tools. *Journal of Pediatrics*, **150**, 510–515.

Klaassen, R.J., Mathias, S.D., Buchanan, G., Bussel, J., Deuson, R., Young, N.L., Collier, A., Bomgaars, L. & Blanchette, V. (2012) Pilot study of the effect of romiplostim on child health-related quality of life (HRQoL) and parental burden in immune thrombocytopenia (ITP). *Pediatric Blood Cancer*, **58**, 395–398.

Klaassen, R.J., Blanchette, V., Burke, T.A., Wakefield, C., Grainger, J.D., Gaedicke, G., Riedlinger, A., Dufort, G., Citrin, E., Reguerre, Y., Pellier, I., Curtis, C. & Young, N.L. (2013) Quality of life in childhood immune thrombocytopenia: international validation of the kids' ITP tools. *Pediatric Blood Cancer*, **60**, 95–100.

Kühne, T., Blanchette, V., Buchanan, G.R., Ramenghi, U., Donato, H., Tamminga, R.Y., Rischewski, J., Berchtold, W. & Imbach, P.; Intercontinental Childhood ITP Study Group. (2007) Splenectomy in children with idiopathic thrombocytopenic purpura: a pro- spective study of 134 children from the Intercontinental Childhood ITP Study Group. *Pediatric Blood Cancer*, **49**, 829–834.

Kuter, D.J., Rummel, M., Boccia, R., Macik, B.G., Pabinger, I., Selleslag, D., Rodeghiero, F., Chong, B.H., Wang, X. & Berger, D.P. (2010) Romiplostim or standard of care in patients with immune thrombocytopenia. *New England Journal of Medicine*, **363**, 1889–1899.

Kuter, D.J., Bussel, J.B., Newland, A., Baker, R.I., Lyons, R.M., Wasser, J., Viallard, J.F., Macik, G., Rummel, M., Nie, K. & Jun, S. (2013) Long-term treatment with romiplostim in patients with chronic immune thrombocytopenia: safety and efficacy. *British Journal of Haematology*, **161**, 411–423.

Larsen, O.H., Stentoft, J., Radia, D., Ingerslev, J. & Sørensen, B. (2013) Combination of recombinant factor VIIa and fibrinogen corrects clot formation in primary immune thrombocytopenia at very low platelet counts. *British Journal of Haematology*, **160**, 228–236.

Liang, Y., Zhang, L., Gao, J., Hu, D. & Ai, Y. (2012) Rituximab for children with immune thrombocytopenia: a systematic review. *PLoS One*, 7, e36698.

Lilleyman, J.S. (1994) Intracranial haemorrhage in idiopathic thrombocytopenic purpura. *Archives of Disease in Childhood*, 74, 251–253.

Maddrey, W.C., Cheng, G., Khelif, A., Wroblewski, S.L. & Brainsky, A. (2009) Evaluation of hepatobiliary parameters during eltrombopag treatment in patients with chronic immune thrombocytopenic purpura. *Blood (ASH Annual Meeting Abstracts)*, 114, 2410.

Mantadakis, E. & Buchanan, G.R. (2000) Elective splenectomy in children with idiopathic thrombocytopenic purpura. *Journal of Pediatric Hematology Oncology*, 22, 148–153.

Neunert, C.E., Buchanan, G.R., Imbach, P., Bolton-Maggs, P.H., Bennett, C.M., Neufeld, E.J., Vesely, S.K., Adix, L., Blanchette, V.S. & Kühne, T. (2008) Intercontinental Childhood ITP Study Group Registry II Participants. Severe hemorrhage in children with newly diagnosed immune thrombocytopenic purpura. *Blood*, 112, 4003–4008.

Neunert, C.E., Buchanan, G.R., Blanchette, V., Barnard, D., Young, N.L., Curtis, C. & Klaassen, R.J. (2009) Relationships among bleeding severity, health-related quality of life, and platelet count in children with immune thrombocytopenic purpura. *Pediatric Blood Cancer*, 53, 652–654.

Neunert, C., Lim, W., Crowther, M., Cohen, A., Solberg, L. Jr & Crowther, M.A.; American Society of Hematology. (2011) The American Society of Hematology 2011 evidence-based practice guideline for immune thrombocytopenia. *Blood*, 117, 4190–4207.

Neunert, C., Buchanan, G.R., Imbach, P., Bolton-Maggs, P.H.B., Bennett, C.M., Neufeld, E., Vesely, S.K., Adix, L., Blanchette, V.S. & Kühne, T. (2013) Bleeding manifestations and management of children with persistent and chronic immune thrombocytopenia: data from the Intercontinental Cooperative ITP Study Group (ICIS). *Blood*, 121, 4457–4462.

Paling, A. & Stefan, D.C. (2008) Idiopathic thrombocytopenic purpura in childhood: a 10-year audit. *Hematology*, 13, 175–180.

Patel, V.L., Mahévas, M., Lee, S.Y., Stasi, R., Cunningham-Rundles, S., Godeau, B., Kanter, J., Neufeld, E., Taube, T., Ramenghi, U., Shenoy, S., Ward, M.J., Mihatov, N., Patel, V.L., Bierling, P., Lesser, M., Cooper, N. & Bussel, J.B. (2012) Outcomes 5 years after response to rituximab therapy in children and adults with immune thrombocytopenia. *Blood*, 119, 5989–5995.

Provan, D., Stasi, R., Newland, A.C., Blanchette, V.S., Bolton-Maggs, P., Bussel, J.B., Chong, B.H., Cines, D.B., Gernsheimer, T.B., Godeau, B., Grainger, J., Greer, I., Hunt, B.J., Imbach, P.A., Lyons, G., McMillan, R., Rodeghiero, F., Sanz, M.A., Tarantino, M., Watson, S., Young, J. & Kuter, D.J. (2010) International consensus report on the investigation and management of primary immune thrombocytopenia. *Blood*, 115, 168–186.

Psaila, B., Petrovic, A., Page, L.K., Menell, J., Schonholz, M. & Bussel, J.B. (2009) Intracranial hemorrhage (ICH) in children with immune thrombocytopenia (ITP): study of 40 cases. *Blood*, 114, 4777–4783.

Rodeghiero, F. & Ruggeri, M. (2012) Short- and long-term risks of splenectomy for benign haematological disorders: should we revisit the indications? *British Journal of Haematology*, 158, 16–29.

Rodeghiero, F., Stasi, R., Gernsheimer, T., Michel, M., Provan, D., Arnold, D.M., Bussel, J.B., Cines, D.B., Chong, B.H., Cooper, N., Godeau, B., Lechner, K., Mazzucconi, M.G., McMillan, R., Sanz, M.A., Imbach, P., Blanchette, V., Kühne, T., Ruggeri, M. & George, J.N. (2009) Standardization of terminology, definitions and outcome criteria in immune thrombocytopenic purpura of adults and children: report from an International Working Group. *Blood*, 113, 2386–2393.

Rosthoj, S., Rajamtie, J., Treutiger, I., Zeller, B., Tedgard, U. & Henter, J. (2012) Duration and morbidity of chronic immune thrombocytopenic purpura in children: five-year follow-up of a Nordic cohort. *Acta Paediatrica*, 101, 761–766.

Russo, G., Miraglia, V., Branciforte, F., Matarese, S.M., Zecca, M., Bisogno, G., Parodi, E., Amendola, G., Giordano, P., Jankovic, M., Corti, A., Nardi, M., Farruggia, P., Battisti, L., Baronci, C., Palazzi, G., Tucci, F., Ceppi, S., Nobili, B., Ramenghi, U., De Mattia, D. & Notarangelo, L.; AIEOP-ITP Study Group. (2011) Effect of eradication of *Helicobacter pylori* in children with chronic immune thrombocytopenia: a prospective, controlled, multicenter study. *Pediatric Blood Cancer*, 56, 273–278.

Salama, A., Rieke, M., Kiesewetter, H. & von Depka, M. (2009) Experiences with recombinant FVIIa in the emergency treatment of patients with autoimmune thrombocytopenia: a review of the literature. *Annals of Hematology*, 88, 11–15.

Saleh, M.N., Bussel, J.B., Cheng, G., Meyer, O., Bailey, C.K., Arning, M. & Brainsky, A.; on behalf of the EXTEND Study Group. (2013) Safety and efficacy of eltrombopag for treatment of chronic immune thrombocytopenia: results of the long-term, open-label EXTEND study. *Blood*, 121, 537–545.

Sarpatwari, A., Watson, S., Erqou, S., Anderson, H., Grainger, J., Higgins, J.P. & Newland, A.C. (2010a) Health-related lifestyle in adults and children with primary immune thrombocytopenia (ITP). *British Journal of Haematology*, 151, 189–191.

Sarpatwari, A., Provan, D., Erqou, S., Sobnack, R., David Tai, F.W. & Newland, A.C. (2010b) Autologous 111 In-labelled platelet sequestration studies in patients with primary immune throm-

bocytopenia (ITP) prior to splenectomy: a report from the United Kingdom ITP Registry. *British Journal of Haematology*, 151, 477–487.

Semple, J.W., Italiano, J.E. Jr & Freedman, J. (2011) Platelets and the immune continuum. *Nature Reviews Immunology*, 11, 264–274.

Shirahata, A., Fujisawa, K., Ishii, E., Ohta, S., Sako, M., Takahashi, Y., Taki, M., Mimaya, J., Kubota, M., Miura, T., Kitazawa, J., Kajiwara, M. & Bessho, F.A. (2009) A nationwide survey of newly diagnosed childhood idiopathic thrombocytopenic purpura in Japan. *Journal of Pediatric Hematology Oncology*, 31, 27–32.

So, M.Y., Li, C.H., Lee, A.C. & Kwong, N.S. (2013) Intracranial haemorrhage among Chinese children with immune thrombocytopenia in a Hong Kong regional hospital. *Hong Kong Medical Journal*, 19, 129–134.

Tamminga, R., Berchtold, W., Bruin, M., Buchanan, G.R. & Kühne, T. (2009) Possible lower rate of chronic ITP after IVIG for acute childhood ITP an analysis from registry I of the Intercontinental Cooperative ITP Study Group (ICIS). *British Journal of Haematology*, 146, 180–184.

Thomsen, R.W., Schooten, W.M., DrK, Farkas., Riis, A., Jacobsen, J., Fryzek, J.P. & Sørensen, H.T. (2009) Risk for hospital contract with infection in patients with splenectomy. *Annals of Internal Medicine*, 151, 546–555.

Thomsen, R.W., Schhnen, W.M., Farkas, D.K., Riis, A., Fryzek, J.P. & Sørensen, H.T. (2010) Risk of venous thromboembolism in splenectomized patients compared with the general population and appendectomized patients: a 10-year nationwide cohort study. *Journal of Thrombosis and Haemostasis*, 8, 1413–1416.

Treutiger, I., Rajantie, J., Zeller, B., Henter, J.I., Elinder, G. & Rosthøj, S.; NOPHO ITP Study Group. (2007) Does treatment of newly diagnosed idiopathic thrombocytopenic purpura reduce morbidity? *Archives of Diseases in Childhood*, 92, 704–707.

Young, M., Thomse, R.W., Schoonen, W.M., Farkas, D.K., Riis, A., Fryzek, J.P. & Sorensen, H.T. (2010) Mortality risk in splenectomised patients: a Danish population-based cohort study. *European Journal of Internal Medicine*, 21, 12–16.

Yri, O.E., Torfoss, D., Hungnes, O., Tierens, A., Waalen, K., Nordøy, T., Dudman, S., Kilander, A., Wader, K.F., Ostenstad, B., Ekanger, R., Meyer, P. & Kolstad, A. (2011) Rituximab blocks protective serologic response to influenza A (H1N1) vaccination in lymphoma patients during or within 6 months after treatment. *Blood*, 118, 6769–6771.

Zilber, R., Bortz, A.P., Yacobovich, J., Yaniv, I. & Tamary, H. (2012) Analysis of health-related quality of life in children with immune thrombocytopenia and their parents using the kids' ITP tools. *Journal of Pediatric Hematology and Oncology*, 34, 2–5.