Diagnosis and management of immune thrombocytopenia in childhood

Thomas Kühne
UKBB Universitäts-Kinderspital, Oncology/Hematology, Basel, Switzerland

Summary
Evidence-based medicine is growing in immune thrombocytopenia (ITP), but solid clinical data are still lacking in many areas. A majority of children has self-limited ITP, but chronic symptomatic ITP exists also in pediatrics. Management includes a watch-and-wait strategy for children with newly diagnosed ITP and no or mild bleeding, and immunoglobulins and corticosteroids, if more bleeding and mucous membrane involvement is present. Treatment endpoints differ in clinical research and in clinical practice. The requirement of platelet enhancing drugs needs to be better defined in guidelines. Second-line therapies for children are rarely required and include thrombopoietin-receptor agonists, rituximab, dexamethasone and immunosuppressants. Thrombopoietin-receptor agonists are successful in adult but also in pediatric ITP. The strategical position of splenectomy differs from that in adults. Although effective in children it is less frequently used because of its life-long cumulative risk of infectious diseases and a higher potential of spontaneous remission in ITP, providing a strong argument to defer splenectomy. The rarity of ITP makes clinical research expensive.

Keywords
immune thrombocytopenia, pediatrics, platelets, management

Schlüsselwörter
Immunthrombozytopenie, Pädiatrie, Thrombozyten, Therapie

Zusammenfassung

Immune thrombocytopenia (ITP) is an autoimmune-mediated acquired bleeding disorder occurring in children and adults (1). Patients without a known etiology or trigger for thrombocytopenia (platelet count <100×10^9/l) have primary ITP, whereas secondary ITP is triggered by diseases (e.g. infectious, lymphoproliferative and rheumatological disorders) or immunodeficiencies (2, 3). Additionally, many drugs are capable to cause thrombocytopenia.

Primary ITP cannot be proven by laboratory tests and thus is a diagnosis of exclusion. Differential diagnostic considerations are important during the whole course of thrombocytopenia.

Pediatric ITP occurs in all age groups. Besides some similarities in pathophysiology, presentation and management there exist specific clinical characteristics at different ages (4). These differences consist of clinical features, such as

- clinical presentation,
- co-morbidities,
- bleeding signs,
- natural history,
- sex and
- health-related quality of life (HR-QoL) (5–7).

During the last 20 years a large body of knowledge has been accumulated with consequences for patient management. Some children – but also some adults – don’t need any treatment (watch-and-wait strategy), whereas standard therapy, including corticosteroids and intravenous high-dose immunoglobulins (IVIG), is administered to symptomatic patients.

There are new drugs which have been studied intensely and that were – in contrast to the traditional ones – introduced
with evidence-based principles. Their strategic position remains to be explored. This review summarizes the diagnosis and management of children with primary ITP.

**Definitions**

In 2007, an international working group (IWG) met at Vicenza, Italy, and harmonized the language of ITP (2). Definitions of the disease were achieved by a consensus process and became a prerequisite to assess and compare results of clinical research.

ITP is diagnosed in a patient with or without bleeding signs and in an otherwise healthy state with isolated thrombocytopenia without any other changes in complete blood count and differentiation of blood cells.

Primary ITP is a diagnosis of exclusion with a long list of differential diagnostic considerations. The vagueness of the diagnosis creates many clinical and research problems, e.g.:
- when and which laboratory tests need to be done,
- when they should be repeated,
- design of clinical trials and
- inclusion/exclusion of study patients.

Although the term “idiopathic” is adequate for ITP, it has been realized that the immune system plays a major role in disease process, and therefore “idiopathic” was replaced by “immune”. Furthermore, “purpura” was abandoned because there are patients with ITP who do not bleed. The IWG proposed therefore to change ITP to immune thrombocytopenia, and maintain the abbreviation “ITP”.

There are three forms of ITP based on the duration of thrombocytopenia:
1. **newly diagnosed ITP** (first 3 months): “Acute ITP” should not be used anymore, because it doesn’t describe the self-limited form of ITP precisely, and because of its retrospective aspect.
2. **persistent ITP** (3–12 months): It reflects the appreciation of the high potential of improvement of ITP during the first year after diagnosis (8, 9).
3. **chronic ITP** (>12 months)

**Severe ITP** is defined by the presence of bleeding symptoms at presentation sufficient to mandate treatment, or occurrence of new bleeding symptoms during the course, requiring additional therapeutic intervention with a different platelet-enhancing agent or an increased dose (2).

**Refractory ITP** refers to adult patients, who failed splenectomy and have severe ITP, or who are at risk of bleeding and require therapy. In children a consensus regarding refractory ITP could not yet be achieved, because
- splenectomy is contraindicated in young children and
- a clear definition at which age a splenectomy can be performed with a balanced risk for overwhelming infectious diseases is absent.

**Epidemiology**

ITP is a rare autoimmune disorder and occurs in its primary form in approx. 3–5 per 100 000 children per year, depending on age and gender but also on seasonal and regional factors (10–13). Interestingly, in infants – and less frequently in young children – ITP occurs more often in boys. The reasons therefore are unknown (14, 15). During school age and adolescence there is no gender difference, whereas female patients are more often seen in adults. However, in patients >65 years there is again a higher occurrence in men than in women (12, 13). ITP exhibits a first peak between the age of 1 and 6 years (14). Secondary ITP is rare in children and its occurrence raises with age, although epidemiologically not well investigated.

The different age peaks and gender distribution at various ages suggest different pathophysiological mechanisms.

**Pathophysiology and Pathogenesis**

The knowledge of the pathophysiological mechanisms of ITP has grown and is important because of its significance as a basis for an adequate management and to find better therapies. Several mechanisms have been discussed and resulted in a better understanding of ITP. Nonetheless, the specific causes of loss of tolerance in this autoimmune disease are still poorly understood, as well as how appropriate treatments should be directed to restore physiological immunocompetence.

The different forms of ITP with a broad spectrum – from self-limited, spontaneously remitted ITP to long-lasting, refractory, severe ITP – suggest different pathophysiological mechanisms and a distortion of regulatory systems. Although it has been shown that autoantibodies, most frequently of the IgG type, play an important role in the development of thrombocytopenia, there are also other immune mechanisms.

In approximately one third of all patients autoantibodies cannot be detected (16).

T-cells play an important role both in autoantibody production by T-helper cells (Th), but also as cytotoxic T-cells that contribute to the destruction of platelets. In patients with ITP a dysbalanced cytokine pattern towards Th1-cells (interleukin-2 and interferon-gamma) can be typically seen. Additionally, it has been shown that CD8+ T-cells are capable to lyse autologous platelets in vitro (17), which has been demonstrated by other groups (18, 19). Immune dysregulation, resulting in T- and B-regulatory cell disturbances, plays also an important role (20, 21). There is evidence indicating that some specific immune cells may induce autoimmune diseases, such as
- Th17,
- Th22 and
- T-follicular helper cells (22, 23).

There are also non-immune mechanisms which may trigger ITP. Oxidative stress resulting in over-production of reactive oxygen species and deficient antioxidant defense mechanisms may reflect such a process (24). Although ITP is an acquired autoimmune disease, familial ITP has also been reported and suggests predisposing factors, secondary ITP or thrombocytopenia other than ITP (25–28). An example represents the autoimmune lymphoproliferative syndrome, which presents with autoimmune cytopenia, mainly thrombocyte- and gra-
Clinical presentation

Bleeding

Primary ITP in children often appears as bleeding disorder with an abrupt onset of skin bleedings (e.g., petechiae or subcutaneous hematomas) within hours that can be accompanied by mucosal bleeding. Traditionally, „dry bleeding” stands for skin bleeding only, and „wet bleeding” if mucous membranes are involved. The Pediatric and Adult Registry on chronic ITP (PARC-ITP) has demonstrated that there are children and adults without bleeding (9 and 31%, respectively), and mucous membranes are less often involved (32).

Recently, it has been shown that occult bleeding is more frequent than anticipated (33).

An insidious onset of bleeding within days and weeks is a typical manifestation of ITP in adults. However, it also occurs in children and is associated with chronic ITP. It has also been shown that besides an abrupt onset age younger than 10 years predicts resolution of ITP (34).

Bleeding phenotype in patients with ITP depends on
- number of platelets,
- function of platelets,
- endogenous factors (e.g. inherited defects of the haemostatic system) and
- exogenous factors (e.g. drugs or infections interfering with haemostasis).

Platelet function measurement in patients with thrombocytopenia is a highly sophisticated task, and several groups have demonstrated an association of impaired platelet function and bleeding severity (35–37). Although pediatric and adult ITP differs in many clinical aspects, there are also similarities which have been shown by the PARC-ITP Registry. The number of patients without bleeding at time of diagnosis, bleeding type and severity of thrombocytopenia did not differ much (32). Nonetheless, bleeding during the course of ITP can be very different in children and adults.

Intracranial haemorrhage (ICH)

In a systematic review, ICH has been found to be more common in adults, and other severe non-ITP bleeding is more common in children occurring at all stages of ITP. However, bleeding severity is not well defined (38).

The platelet count of children with ITP at first presentation is less than $20 \times 10^9 / l$ in approximately 80%. Nonetheless, major haemorrhage is rare – also in its broad definition, that has been used by the Intercontinental Childhood ITP Study Group (ICIS) Registry II (39, 40), such as intracranial or other overt internal or mucous membrane bleeding, which results in anaemia or requires local treatment to stop haemorrhage.

ICIS Registry II was designed to investigate bleeding and platelet counts in children with ITP based on the hypothesis that major haemorrhage in pediatric ITP is uncommon during 2 years after diagnosis. At diagnosis 2.9% of the children experienced a severe haemorrhage with one non-fatal ICH (0.15% incidence) and subsequent development of new severe bleeding was very rare and did not depend on initial treatment (39).

Most information on ICH in children with ITP is derived from registries and retrospective data. It appears that it is associated with a platelet count of less than $20 \times 10^9 / l$ in 90% of the patients, and less than $10 \times 10^9 / l$ in 75%.

However, a clear correlation between bleeding and platelet count has not been demonstrated (41, 42).

ICH does not only occur at the time when ITP is diagnosed, but also later when severe thrombocytopenia exists. Head trauma and haematuria was found to be prominent features in an U. S. nationwide survey (42). It can be estimated that ICH occurs in less than 1% of children with ITP.

Infectious diseases

Infectious diseases of the upper respiratory and the gastrointestinal tract are frequently seen days or weeks before ITP in children. The ICIS Registry I and Nordic Study have demonstrated that 50% of the children exhibited an infectious disorder within approximately 21 days from diagnosis of ITP, and mainly in children aged 1–10 years (4, 43). These infections occur at the same peak age as ITP does.

It is still unclear whether infectious disorders are etiological significant for ITP. It has been demonstrated that measles-mumps-rubella (MMR) vaccine and MMR plus varicella vaccine may trigger ITP (44, 45).

Frequency of clinical symptoms

The majority of children have self-limited ITP, and ICIS Registry II has shown that remission occurred in
- 37% of the thrombocytopenic children between 28 days and 6 months after initial diagnosis,
- 16% between 6 and 12 months and
- 24% between 12 and 24 months (40).

In registries the percentage of children with chronic ITP is approximately 30%. However, patients with clinical symptoms are much more rare. A Nordic cohort of children with chronic ITP has shown that
- one half of the patients recovered 5 years after diagnosis,
- more than a half of them never required hospitalization, and
- serious bleeding episodes occurred in <10%, always when a platelet count of <20 $\times 10^9 / l$ was present (9).

This high remission rate was also demonstrated in a Korean cohort (46).

Diagnosis and differential diagnosis

Primary ITP is a diagnosis of exclusion. A threshold platelet count of less than $100 \times 10^9 / l$ was established by the IWG based on the observation that individuals
with a platelet count of 100–150 × 10^9/l have a low probability of developing severe thrombocytopenia, and that platelet values of 100–150 × 10^9/l are frequently found in individuals of non-Western origin (2).

Although diagnosis of primary ITP is simple, the differential diagnostic considerations are complex. Any pathological finding except bleeding questions the diagnosis of primary ITP. It is based on clinical and laboratory information:

- ITP occurs in children with or even without haemorrhage, who are otherwise healthy.
- Family history is usually negative regarding bleeding disorders. If positive, differential diagnostic considerations should be undertaken, which is described elsewhere (47–49).
- Physical examination does not reveal any abnormalities except haemorrhagic diathesis consisting of petechiae and subcutaneous hematomas, and sometimes mucous membrane bleeding.
- Complete blood count is normal except for the platelet count.
- Haemoglobin could be reduced in presence of bleeding.
- Blood smear is normal, and frequently large platelets can be observed.

Additional tests may be necessary if patient/family history, physical examination and/or laboratory results are not in agreement with the diagnosis of primary ITP. According to the current guidelines of the American Society of Hematology (ASH), bone marrow examination is not needed in the absence of additional findings, i.e. in children with the diagnosis of primary ITP, even if corticosteroids will be administered (50). However, it is advisable to perform it if there are any doubts in diagnosis.

**Follow-up diagnostics in persistent and chronic ITP is not standardized and needs an individual approach.**

**Principles of treatment**

Basically, the testing is guided by clinical symptoms. The international guidelines recommend:

- bone marrow investigations if ITP persists without a prior therapeutic response,
- evaluation of infectious diseases in presence of clinical suspicion or high local prevalence,
- antinuclear and anti-phospholipid antibodies (including anti-cardiolipin antibodies), lupus anticoagulant and serum immunoglobulins (IgG, IgM, IgA).

Other considerations should focus on common variable immunodeficiency, autoimmune lymphoproliferative syndrome and many other disorders. According to the ASH guidelines there is insufficient evidence to support a systematic approach to test for such conditions.

Bleeding has been classified with diagnostic and predictive significance but also as treatment endpoint. The development of bleeding scores and their value as bedside test is challenging. Bleeding is the result of many factors and is a dynamic process that can change within minutes. It thus reflects a highly individual and complex characteristic of a given patient.

**HR-QoL** appears to be an attractive treatment endpoint, which may be categorized and expressed as a score. As in other disciplines such as inherited bleeding disorders or oncology, the development and validation of tools to measure HR-QoL are complex and challenging and still far away from clinical practice (56–58). Pediatric tools specific to ITP were developed and practiced in clinical trials (59).

Whether bleeding scores are useful tools in clinical practice and reflect therapeutic requirements of patients with ITP has not been established and is still a matter of discussion (51–54). Bleeding as a treatment endpoint has the potential to change therapeutic requirements (55).

**Treatment options**

**Life-threatening bleeding**

For children with life-threatening bleeding, evidence-based clinical data are lacking. But there is a strong consensus to administer immediately...
• platelet transfusions,
• intravenous high-dose immunoglobulins (1g/kg) and
• intravenous methylprednisolone (30mg/kg for 3 days).

In other situations platelet transfusions are not indicated.

Emergency splenectomy may be performed; however, there are not sufficient data supporting this procedure.

There is limited experience for recombinant factor VIIa, also in combination with fibrinogen (62, 63).

**Newly diagnosed ITP**

Whether a child with newly diagnosed ITP will receive drug treatment or be observed without depends more on clinical signs, such as bleeding, than on platelet count. The revised 2011 ASH practice guidelines (50) and the International guidelines (60) were the first ones that clearly recommended watchful waiting for children with no or mild bleeding. Former guidelines defined such mild bleeding as skin manifestations only (e.g. bruising or petechiae), and stated that treatment decision could be made regardless of the platelet count (50).

In presence of more bleeding, particularly of the mucous membranes, it is currently recommended to administer first-line treatment. It is a matter of discussion whether such "wet" bleeding really represents a higher risk for life-threatening bleeding than "dry" bleeding only.

First-line treatment is shown in ▶Tab. 1. Recently, it has been shown that dexamethasone is more effective in inducing a higher incidence of overall initial response than prednisone in adults with newly-diagnosed ITP. This demonstrates the incomplete knowledge of first-line therapies (64).

**Persistent ITP**

This category of ITP has been created to point out the high potential of patients with ITP who will improve or recover within 3–12 months after diagnosis. Treatment indications and options are the same as for children with newly diagnosed ITP.

Splenectomy is not recommended for children with this form of ITP.

**Chronic ITP**

Symptomatic children with chronic ITP requiring treatment are a small group of patients. Short courses of first-line treatments, including watch-and-wait strategy, are frequently helpful.

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Administration</th>
<th>Dose</th>
<th>Interval</th>
<th>Pros</th>
<th>Cons</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>watch-and-wait</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>• same rate of remission expected as for drug treatment</td>
<td>time-consuming conversation</td>
<td>based on practice guidelines (46, 56)</td>
</tr>
<tr>
<td>IVIG</td>
<td>i. v.</td>
<td>0.8–1.0 g/kg</td>
<td>once daily, 1–2 x</td>
<td>• platelet response within 24–48 hours</td>
<td>blood product</td>
<td>consider premedication with paracetamol</td>
</tr>
<tr>
<td>Prednisone</td>
<td>oral</td>
<td>1–2 mg/kg</td>
<td>single morning dose or 2–3 daily doses for 14 days and 1 week of tapering</td>
<td>• no need for hospitalization</td>
<td>side effects</td>
<td>platelet response slower than after IVIG (2–7 days)</td>
</tr>
<tr>
<td>Anti-D</td>
<td>i. v.</td>
<td>75 µg/kg</td>
<td>single dose</td>
<td>• efficacy</td>
<td>side effects</td>
<td>not used in Europe anymore</td>
</tr>
</tbody>
</table>

i. v.: intravenous; DAT: direct antiglobulin test; IVIG: intravenous immunoglobulins

© Schattauer 2017

Hämostaseologie 1/2017
<table>
<thead>
<tr>
<th>Intervention</th>
<th>Administration</th>
<th>Dose</th>
<th>Dose interval</th>
<th>Pros</th>
<th>Cons</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dexamethasone</td>
<td>oral</td>
<td>28 mg/m² / day</td>
<td>3 doses / day × 4 for 6 months</td>
<td>availability, cheap, high short-term efficacy, deferral of splenectomy</td>
<td>side effects, low long-term efficacy</td>
<td>not licensed for children, doses from reference (60)</td>
</tr>
<tr>
<td>Eltrombopag</td>
<td>oral</td>
<td>25 mg (1–5 years)</td>
<td>once daily</td>
<td>efficacy, safety profile, deferral of splenectomy</td>
<td>efficacy restrictions, side effects, expensive, long-term safety: limited experience</td>
<td>licensed for children; currently as second-line therapy in chronic ITP, doses from reference (93)</td>
</tr>
<tr>
<td>Romiplostim</td>
<td>s. c.</td>
<td>dose not yet established, 1–10 µg/kg in adults</td>
<td>once weekly</td>
<td>efficacy, safety profile, deferral of splenectomy</td>
<td>parenteral administration, side effects, expensive, long-term safety: limited experience</td>
<td>not licensed for children; currently as second-line therapy in adults with chronic ITP</td>
</tr>
<tr>
<td>Rituximab</td>
<td>i. v.</td>
<td>375 mg/m², dose not established</td>
<td>once weekly × 4</td>
<td>efficacy (Cave: response may be delayed to 8 weeks)</td>
<td>side effects, long-term efficacy limited in adults, not known in children</td>
<td>not licensed for children</td>
</tr>
<tr>
<td>Azathioprine, Cyclosporine A, Cyclophosphamide, Danazol, Dapsone, Mycophenolate mofetil, Vinca alkaloids</td>
<td>i. v./oral</td>
<td>doses not established</td>
<td>different regimens</td>
<td>may be effective in individual patients</td>
<td>experience limited, side effects, necessitating anti-infective measures</td>
<td>individual approach, not licensed for children</td>
</tr>
<tr>
<td>Splenectomy</td>
<td>open or laparoscopic surgery</td>
<td>—</td>
<td>—</td>
<td>efficacy in 80%, long-term response decreasing, potential of cure, standard procedure, widely available</td>
<td>contraindicated in young children (approx. &lt; 5 years), complications (infections, thrombosis), life without spleen</td>
<td>rarely performed in children, difficult to be studied, prevention from infections (vaccinations, antibiotic prophylaxis)</td>
</tr>
</tbody>
</table>

s. c.: subcutaneous; i. v.: intravenous; ITP: immune thrombocytopenia

The aim of the treatment in chronic ITP is not to achieve a normal platelet count but to avoid bleeding and to increase HR-QoL.

Treatment refractoriness to first-line therapy in children with chronic ITP is rarely seen and if so, an individual approach is needed (65). Because of the fact that chronic symptomatic ITP is that rare it is extremely hard to generate evidence-based data.

### Splenectomy

Although splenectomy is an effective treatment in children (66, 67) and has the potential to cure the patient, it has not the same strategical significance as for adults (68). Thus, treatment refractoriness in pediatric patients has not been defined by the IWG and still awaits consensus. In adult patients it is defined by failure to splenectomy or a relapse thereafter and the presence of severe ITP or a risk of bleeding that requires therapy (2).
In children splenectomy is associated with an increased risk for overwhelming infections by encapsulated bacteria, such as pneumococci, hemophilus influenzae or meningococci.

The risk for infections in children after splenectomy increases with decreasing age. Whether the thrombotic risk is different in children than in adults is not clear.

The care of splenectomized children is not trivial. Patients should be educated to the lifelong risks and aspects of living without a spleen, e.g.
- vaccinations,
- antibiotic prophylaxis,
- planning travel aids,
- regular visits,
- carrying medical information etc.

In addition, surgical complications and the risk of a relapse, poor or no response have to be considered. The probably higher potential of spontaneous improvement and even cure in children is a further argument to defer splenectomy. Mainly demonstrated in adults, there are several published ways to defer splenectomy (69–71).

In summary, the poorly studied timing and indication of splenectomy, its risk of complications and the unforeseen potential of remission make splenectomy an effective but highly questionable procedure in children (72).

**Second-line therapy**

Second-line therapy (Tab. 2) is rarely used in children. Thrombopoietin receptor agonists (TPO-RAs) are successful drugs in adults and are also studied in children (73–75). Recently, Eltrombopag was licensed for children and Romiplostim is still under investigation. These drugs appear to have similar response rates and favorable safety profiles compared with adults (76, 77).

There is increasing knowledge of long-term safety in adults (78–80) but not in children. Potential and theoretical risks include
- thromboembolic events that may be triggered by the TPO-RAs directly or in relation to comorbidity and concomitant drugs,
- stimulation of bone marrow reticulin and collagen fibers,
- stimulation of malignant cells and induction of malignancy, extramyeloid reactions, platelet activation, and hematopoietic stem cell depletion.

Long-term safety of TPO-RAs is an important area of future pediatric clinical research. Sustained response after stopping TPO-RAs in adults has been observed and will be studied (81–83). Other second-line therapies include
- dexamethasone,
- rituximab and immunosuppressants.

Oral pulsed high-dose dexamethasone therapy has been attempted to modulate the immune system with regular administrations. Different dose regimens have been used (60, 84, 85). Adverse effects of dexamethasone can be substantial.

Rituximab has been studied in adult patients successfully with an acceptable safety profile (86) that could be reproduced in children (87–89). However, there are no comparative studies and experience of this drug for children is still limited.

Addition of dexamethasone to rituximab has been shown to increase the effect (90). Combination therapies of rituximab, dexamethasone and cyclosporine, and TPO-RAs with rituximab in adult and also pediatric patients with refractory ITP have been studied with some success and need to be studied in more details (91, 92). However these regimens are reserved for most severely affected patients and may be toxic, thus their benefit must be carefully weighed against their risks.

Immunosuppressants have been less well studied in children than in adults. Drugs with more favourable safety profiles, such as the TPO-RAs, appear to be more attractive and may play an important role in children with chronic ITP who do not respond to first-line therapies.

**Reference**

There are several challenges and questions regarding pediatric ITP. The small number of pediatric patients necessitating international research, the limited resources for investigator-driven research and the difficulties to coordinate research represent challenges.

There are internationally active groups, e.g.
- IWG (2),
- ICIS (www.itpbasel.ch) and working groups of societies, such as the European Haematology Association.

It is to be hoped that future activities will give answers to questions, such as
- etiology and pathophysiology of ITP,
- prediction of the form of ITP (self-limited or chronic),
- diagnostic algorithms for children with persistent and chronic ITP,
- definitions of pediatric ITP, and clinical trials exploring efficacy and safety of newer drugs in children.

**Conflict of interest**

The author declares that he received research funds from Amgen and that he is a member of an advisory board of UCB CELLTECH.

**References**


50. Heitink-Pollé KMJ, Haverman L, Annink KV et al. Health-related quality of life in children with
Kühne T. Immune thrombocytopenia in childhood

90. Bussel JB, Lee CS, Seery C et al. Rituximab and three dexamethasone cycles provide responses similar to splenectomy in women and those with immune thrombocytopenia of less than two years duration. Haematologica 2014; 99: 1264–1271.