

Diagnosis and management of immune thrombocytopenia in childhood

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Keywords

immune thrombocytopenia, pediatrics, platelets, management

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.

Schlüsselwörter

Immunthrombozytopenie, Pädiatrie, Thrombozyten, Therapie

Zusammenfassung

Die Immunthrombozytopenie (ITP) hat einen eindrücklichen Wissenszuwachs erfahren, aber klinische Daten fehlen noch in vielen Bereichen. Bei vielen Kindern ist die ITP eine selbstlimitierte Krankheit und muss nicht mit Medikamenten behandelt werden, falls keine oder nur eine milde Blutung vorliegt. Für Kinder mit stärkeren oder Schleimhautblutungen stehen Immunglobuline und Steroide zur Verfügung. Behandlungsziele und Therapienotwendigkeit von Kindern mit ITP unterscheiden sich in klinischen Studien und im klinischen Alltag. Sie sollten überprüft und in Richtlinien klarer festgelegt werden. Zweitlinien-Therapien werden bei Kindern selten angewendet und beinhalten Thrombopoietin-Rezeptor-Agonisten, Rituximab, Dexamethason und Immunsuppressiva. Thrombopoietin-Rezeptor-Agonisten sind bei Erwachsenen wie auch bei Kindern erfolgreich. Die strategische Stellung der Splenektomie bei Kindern unterscheidet sich von derjenigen bei erwachsenen Patienten: Das lebenslängliche Infektionsrisiko und höhere Remissions-Potenzial sprechen bei Kindern dafür, die Splenektomie zu verschieben. Die Seltenheit der ITP verursacht hohe Forschungskosten.

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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 $<100 \times 10^9/l$) 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. Beside 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-

nulocytopenia, chronic non-malignant lymphoproliferation and secondary malignancies (29). First described in the 1990s, it reflects an inherited abnormality of apoptosis with mutated genes encoding proteins that mediate apoptotic pathways, such as Fas or caspase 10 (30, 31).

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 pa-

tients 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-ICH 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 $100\text{--}150 \times 10^9/l$ have a low probability of developing severe thrombocytopenia, and that platelet values of $100\text{--}150 \times 10^9/l$ 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.

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.

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).

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).

Principles of treatment

Treatment of children and adults with newly diagnosed, persistent and chronic ITP is based on national and international (60) practice guidelines. Some of them are regularly revised (50, 61). In contrast to children with newly diagnosed ITP, the degree of evidence is low for recommen-

dations in children with persistent and particularly chronic ITP.

In this review article, recommendations and suggestions are briefly summarized. The aim of treating children with ITP is to

- prevent life-threatening bleeding,
- stabilize and reduce bleeding, if clinically needed, and
- increase HR-QoL.

Other aims include transiently increasing the platelet count before surgery, deferring splenectomy and avoiding bleeding of patients with comorbidities. Treatment endpoints include

- platelet count,
- bleeding,
- HR-QoL,
- preventing drug treatment side effects,
- reducing the need for rescue and concomitant treatment,
- avoiding of splenectomy, and
- economical aspects.

The platelet count is an easily and rapidly available bedside test. However, its value as an indicator of bleeding is limited, although severe haemorrhage is frequently associated with a platelet count of less than $20 \times 10^9/l$. It has to be demonstrated that bleeding and HR-QoL may better describe patients with ITP and define their therapeutic requirements.

Pre-analytical and analytical difficulties must always be considered, particularly, when the platelet count is low. The questions “Who needs treatment?” and “What is the meaning of treatment requirement in current guidelines?” can only be answered by assessing all clinical and laboratory information, and are highly individual. Many aspects of the management of children with ITP, e.g. treatment endpoint of severe life-threatening bleeding, are hard to study in prospective randomized clinical trials because of the rarity of ITP.

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.

So far, mucous membrane bleeding has not been graded for prognostic purposes and it may be worthwhile to develop and validate such a tool in pediatric patients in order to have a better basis for treatment decisions.

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-diag-

nosed ITP. This demonstrates the incomplete knowledge of first-line therapies (64).

Second-line treatment (► Tab. 2) is rarely needed in children with newly diagnosed ITP. It is indicated in symptomatic children that are not responding to first-line treatment.

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.

Tab. 1 First-line treatment options for children with newly diagnosed ITP with selected pros and cons (50, 60).

Intervention	Administration	Dose	Interval	Pros	Cons	Remarks
watch-and-wait	–	–	–	<ul style="list-style-type: none"> • same rate of remission expected as for drug treatment • no drug related side effects 	<ul style="list-style-type: none"> • time-consuming conversation • experienced physician needed 	based on practice guidelines (46, 56)
IVIG	i. v.	0.8–1.0 g/kg	once daily, 1–2 ×	<ul style="list-style-type: none"> • platelet response within 24–48 hours • diagnostic significance 	<ul style="list-style-type: none"> • blood product • i. v. line needed • infusion over several hours • side effects • price 	consider premedication with paracetamol
Prednisone	oral	1–2 mg/kg	single morning dose or 2–3 daily doses for 14 days and 1 week of tapering	<ul style="list-style-type: none"> • no need for hospitalization • availability • cheap • fast response 	side effects	platelet response slower than after IVIG (2–7 days)
		4 mg/kg	1–3 doses/day for 4 days	see above	see above	see above
Anti-D	i. v.	75 µg/kg	single dose	<ul style="list-style-type: none"> • efficacy • fast administration • no need for hospitalization 	<ul style="list-style-type: none"> • side effects • patient: Rh D+, not splenectomized, not anaemic, DAT negative 	not used in Europe anymore

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

Tab. 2 Second-line treatment options for children with selected pros and cons (50, 60, 65).

Intervention	Administration	Dose	Dose interval	Pros	Cons	Remarks
Dexamethasone	oral	28 mg/m ² /day	3 doses/day × 4 for 6 months	<ul style="list-style-type: none"> availability cheap high short-term efficacy deferral of splenectomy 	<ul style="list-style-type: none"> side effects low long-term efficacy 	not licensed for children, doses from reference (60)
Eltrombopag	oral	<ul style="list-style-type: none"> 25 mg (1–5 years) 50 mg (6–17 years) 25 mg in patients of East Asian descent 	once daily	<ul style="list-style-type: none"> efficacy safety profile deferral of splenectomy 	<ul style="list-style-type: none"> diet restrictions side effects expensive long-term safety: limited experience 	licensed for children; currently as second-line therapy in chronic ITP, doses from reference (93)
Romiplostim	s. c.	dose not yet established, 1–10 µg/kg in adults	once weekly	<ul style="list-style-type: none"> efficacy safety profile deferral of splenectomy 	<ul style="list-style-type: none"> parenteral administration side effects expensive long-term safety: limited experience 	not licensed for children; currently as second-line therapy in adults with chronic ITP
Rituximab	i. v.	375 mg/m ² , dose not established	once weekly × 4	<ul style="list-style-type: none"> efficacy (Cave: response may be delayed to 8 weeks) 	<ul style="list-style-type: none"> side effects long-term efficacy limited in adults, not known in children 	not licensed for children
Azathioprine, Cyclosporine A, Cyclophosphamide, Danazol, Dapsone, Mycophenolate mofetil, Vinca alkaloids	i. v./oral	doses not established	different regimens	<ul style="list-style-type: none"> may be effective in individual patients 	<ul style="list-style-type: none"> experience limited side effects, necessitating anti-infective measures 	individual approach, not licensed for children
Splenectomy	open or laparoscopic surgery	–	–	<ul style="list-style-type: none"> efficacy in 80 %, long-term response decreasing potential of cure standard procedure widely available 	<ul style="list-style-type: none"> contraindicated in young children (approx. <5 years) complications (infections, thrombosis) life without spleen 	<ul style="list-style-type: none"> rarely performed in children, difficult to be studied prevention from infections (vaccinations, antibiotic prophylaxis)

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 haematopoietic 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.

Outlook

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

1. Kühne T. Immune thrombocytopenia (ITP). 1st edition. Bremen: UNI-MED 2010.
2. Rodeghiero F, Stasi R, Gernsheimer T et al. Standardization of terminology, definitions and outcome criteria in immune thrombocytopenic purpura (ITP) of adults and children. Report from an international working group. *Blood* 2009; 113: 2386–2393.
3. Price V. Auto-immune lymphoproliferative disorder and other secondary immune thrombocytopenias in childhood. *Pediatric Blood Cancer* 2013; 60: S12–S14.
4. Kühne T, Buchanan GR, Zimmerman S et al. A prospective comparative study of 2540 infants and children with newly diagnosed idiopathic thrombocytopenic purpura (ITP) from The Intercontinental Childhood ITP Study Group. *J Pediatr* 2003; 143: 605–608.
5. Arnold DM. Bleeding complications in immune thrombocytopenia. *Hematology Am Soc Hematol Educ Program* 2015; 2015: 237–242.
6. Zhou Z, Yang L, Chen Z et al. Health-related quality of life measured by the Short Form 36 in immune thrombocytopenic purpura: a cross-sectional survey in China. *Eur J Haematol* 2007; 78: 518–523.
7. Sarpatwari A, Watson S, Erqou S et al. Health-related lifestyle in adults and children with primary immune thrombocytopenia (ITP). *Br J Haematol* 2010; 151: 189–191.

8. Imbach P, Kühne T, Müller D et al. Childhood ITP: 12 months follow-up data from the prospective registry I of the Intercontinental Childhood ITP Study Group (ICIS). *Pediatr Blood Cancer* 2006; 46: 351–356.
9. Rosthøj S, Rajantie J, Treutiger I et al. Duration and morbidity of chronic immune thrombocytopenic purpura in children: five-year follow-up of a Nordic cohort. *Acta Paediatr* 2012; 101: 761–766.
10. Sutor AH, Harms A, Kaufmehl K. Acute Immune thrombocytopenia (ITP) in childhood: Retrospective and prospective survey in Germany. *Semin Thromb Hemost* 2001; 27: 253–267.
11. Zeller B, Helgestad J, Hellebostad M et al. Immune thrombocytopenic purpura in childhood in Norway: a prospective, population-based registration. *Pediatr Hematol Oncol* 2000; 17: 551–558.
12. Schoonen WM, Kucera G, Coalsen J et al. Epidemiology of immune thrombocytopenic purpura in the General Practice Research Database. *Br J Haematol* 2009; 145: 235–244.
13. Moulis G, Palmaro A, Montastruc JL et al. Epidemiology of incident immune thrombocytopenia: a nationwide population-based study in France. *Blood* 2014; 124: 3308–3315.
14. Kühne T, Imbach P, Bolton-Maggs PHB et al. Newly diagnosed idiopathic thrombocytopenic purpura in childhood: an observational study. *Lancet* 2001; 358: 2122–2125.
15. Yong M, Schoonen WM, Li L et al. Epidemiology of paediatric immune thrombocytopenia in the General Practice Research Database. *Br J Haematol* 2010; 149: 855–864.
16. Warner MN, Moore JC, Warkentin TE et al. A prospective study of protein-specific assays used to investigate idiopathic thrombocytopenic purpura. *Br J Haematol* 1999; 104: 442–447.
17. Olsson B, Andersson PO, Jernas M et al. T-cell-mediated cytotoxicity toward platelets in chronic idiopathic thrombocytopenic purpura. *Nat Med* 2003; 9: 1123–1124.
18. Zhang F, Chu X, Wang L et al. Cell-mediated lysis of autologous platelets in chronic idiopathic thrombocytopenic purpura. *Eur J Haematol* 2006; 76: 427–431.
19. Guo L, Kapur R, Aslam R et al. CD20+ B-cell depletion therapy suppresses murine CD8+ T-cell-mediated immune thrombocytopenia. *Blood* 2016; 127: 735–738.
20. Nishimoto T1, Kuwana M. CD4+CD25+Foxp3+ regulatory T cells in the pathophysiology of immune thrombocytopenia. *Semin Hematol* 2013 Jan; 50: S43S49.
21. Aslam R, Segel GB, Burack R et al. Splenic lymphocyte subtypes in immune thrombocytopenia: increased presence of a subtype of B-regulatory cells. *Br J Haematol* 2016; 173: 159–160.
22. Jernas M, Nookaew I, Wadenvik H, Olsson B. MicroRNA regulate immunological pathways in T-cells in immune thrombocytopenia (ITP). *Blood* 2013; 121: 2095–2098.
23. McKenzie CG, Guo L, Freedman J, Semple JW. Cellular immune dysfunction in immune thrombocytopenia (ITP). *Br J Haematol* 2013; 163: 10–23.
24. Zhang B, Lo C, Shen L et al. The role of vanin-1 and oxidative stress-related pathways in distinguishing acute and chronic pediatric ITP. *Blood* 2011; 117: 4569–4579.
25. Rischewski JR, Imbach P, Paulussen M, Kühne T. Idiopathic Thrombocytopenic Purpura (ITP): Is there a genetic predisposition? *Pediatr Blood Cancer* 2006; 47: 678–680.
26. Buchanan GR. 50 years ago in the *Journal of Pediatrics*: familial idiopathic thrombocytopenic purpura. *J Pediatr* 2013; 162: 704.
27. Drachman JG. Inherited thrombocytopenia: when a low platelet count does not mean ITP. *Blood* 2004; 103: 390–398.
28. Teachey DT, Lambert MP. Diagnosis and management of autoimmune cytopenias in childhood. *Pediatr Clin N Am* 2013; 60: 1489–1511.
29. Teachey DT. New advances in the diagnosis and treatment of autoimmune lymphoproliferative syndrome (ALPS). *Curr Opin Pediatr* 2012; 24: 1–8.
30. Oliveira JB, Blessing JJ, Dianzani U et al. Revised diagnostic criteria and classification for the autoimmune lymphoproliferative syndrome (ALPS): report from the 2009 NIH International Workshop. *Blood* 2010; 116: e35–e40.
31. Price V. Auto-immune lymphoproliferative disorder and other secondary immune thrombocytopenias in childhood. *Pediatr Blood Cancer* 2013; 60: S12S14.
32. Kühne T, Berchtold W, Michaels LA et al. Newly diagnosed immune thrombocytopenia in children and adults, a comparative prospective observational registry of the Intercontinental Cooperative Immune Thrombocytopenia Study Group. *Haematologica* 2011; 96: 1831–1837.
33. Flores A, Buchanan GR. Occult hemorrhage in children with severe ITP. *Am J Hematol* 2016; 91: 287–290.
34. Revel-Vilk S, Yacovich J, Frank S et al. Age and duration of bleeding symptoms at diagnosis best predict resolution of childhood immune thrombocytopenia at 3, 6, and 12 months. *J Pediatr* 2013; 163: 1335–1339.
35. van Bladel ER, Laarhoven AG, van der Heijden LB et al. Functional platelet defects in children with severe chronic ITP as tested with two novel assays applicable for low platelet counts. *Blood* 2014; 123: 1556–1563.
36. Frelinger AL, Grace RF, Gerrits AJ et al. Platelet function tests, independent of platelet count, are associated with bleeding severity in ITP. *Blood* 2015; 126: 873–879.
37. Middelburg RA, Carbaat-Ham JC et al. Platelet function in adult ITP patients can be either increased or decreased, compared to healthy controls, and is associated with bleeding risk. *Hematology* 2016; 21:549–551.
38. Neunert C, Noroozi N, Norman G et al. Severe bleeding events in adults and children with primary immune thrombocytopenia: a systematic review. *J Thromb Haemost* 2014; 13: 457–464.
39. Neunert CE, Buchanan GR, Imbach P et al. Severe hemorrhage in children with newly diagnosed immune thrombocytopenic purpura. *Blood* 2008; 112: 4003–4008.
40. Neunert CE, Buchanan GR, Imbach P et al. Bleeding manifestations and management of children with persistent and chronic immune thrombocytopenia: data from the Intercontinental Cooperative ITP Study Group (ICIS). *Blood* 2013; 121: 4457–4462.
41. Lilleyman JS. Intracranial haemorrhage in idiopathic thrombocytopenic purpura. *Arch Dis Child* 1994; 71: 251–253.
42. Psaila B, Petrovic A, Page LK et al. Intracranial hemorrhage (ICH) in children with immune thrombocytopenia (ITP): study of 40 cases. *Blood* 2009; 114: 4777–4783.
43. Rosthøj S, Hedlund-Treutiger I, Rajantie J et al. Duration and morbidity of newly diagnosed idiopathic thrombocytopenic purpura in children: A prospective Nordic study of an unselected cohort. *J Pediatr* 2003; 143: 302–307.
44. Cecinati V, Principi N, Brescia L et al. Vaccine administration and the development of immune thrombocytopenic purpura in children. *Hum Vaccin Immunother* 2013; 9: 1158–1162.
45. Klein NP, Lewis E, Fireman B et al. Safety of measles-containing vaccines in 1-year-old children. *Pediatrics* 2015; 135: e321–e329.
46. Kim CY, Lee EH, Yoon HS. High Remission Rate of Chronic Immune Thrombocytopenia in Children: Result of 20-Year Follow-Up. *Yonsei Med J* 2016; 57: 127–131.
47. Kühne T, Imbach P. Management of children and adolescents with primary immune thrombocytopenia: controversies and solutions. *Vox Sang* 2013; 104: 55–66.
48. Teachey DT, Lambert MP. Diagnosis and management of autoimmune cytopenias in childhood. *Pediatr Clin N Am* 2013; 60: 1489–1511.
49. Fiore M, Pillois X, Lorrain S et al. A diagnostic approach that may help to discriminate inherited thrombocytopenia from chronic immune thrombocytopenia in adult patient. *Platelets* 2016; 27: 555–562.
50. Neunert C, Lim W, Crowther M et al. The American Society of Hematology 2011 evidence-based practice guideline for immune thrombocytopenia. *Blood* 2011; 117: 4190–4207.
51. Bolton-Maggs PH. Severe Bleeding in idiopathic thrombocytopenic purpura. *J Pediatr Hematol Oncol* 2003; 25: S47–S51.
52. Buchanan GR, Adix L. Grading of hemorrhage in children with idiopathic thrombocytopenic purpura. *J Pediatr* 2002; 141: 683–688.
53. Edslev PW, Rosthøj S, Treutiger I et al. A clinical score predicting a brief and uneventful course of newly diagnosed idiopathic thrombocytopenic purpura in children. *Br J Hematol* 2007; 138: 513–516.
54. Rodeghiero F, Michel M, Gernsheimer T et al. Standardization of bleeding assessment in immune thrombocytopenia: report from the International Working Group. *Blood* 2013; 121: 2596–2606.
55. Khellaf M, Michel M, Schaeffer A et al. Assessment of a therapeutic strategy for adults with severe autoimmune thrombocytopenic purpura based on a bleeding score rather than platelet count. *Haematologica* 2005; 90: 829–832.
56. Klaassen RJ, Blanchette V, Burke TA et al. Quality of life in childhood immune thrombocytopenia: international validation of the kids' ITP tools. *Pediatr Blood Cancer* 2013; 60: 95–100.
57. Grainger JD, Young NL, Blanchette VS, Klaassen RJ. Quality of life in immune thrombocytopenia following treatment. *Arch Dis Child* 2013; 98: 895–897.
58. Heitink-Pollé KMJ, Haverman L, Annink KV et al. Health-related quality of life in children with

- newly diagnosed immune thrombocytopenia. *Haematologica* 2014; 99: 1525–1531.
59. Klaassen RJ, Mathias SD, Buchanan G et al. Pilot Study of the Effect of Romiplostim on Child Health-Related Quality of Life (HRQoL) and Parental Burden in Immune Thrombocytopenia (ITP). *Pediatr Blood Cancer* 2012; 58: 395–398.
 60. Provan D, Stasi R, Newland AC et al. International consensus report on the investigation and management of primary immune thrombocytopenia. *Blood* 2010; 115: 168–186.
 61. George JN, Woolf SH, Raskob GE et al. Idiopathic thrombocytopenic purpura: a practice guideline developed by explicit methods for The American Society of Hematology. *Blood* 1996; 88: 3–40.
 62. Salama A, Rieke M, Kiesewetter H, von Depka M. Experiences with recombinant FVIIa in the emergency treatment of patients with autoimmune thrombocytopenia: a review of the literature. *Ann Hematol* 2009; 88: 11–15.
 63. Larsen OH, Stentoft J, Radia D et al. Combination of recombinant factor VIIa and fibrinogen corrects clot formation in primary immune thrombocytopenia at very low platelet counts. *Br J Haematol* 2013; 160: 228–236.
 64. Wie Y, Ji X, Wang Y et al. High-dose dexamethasone vs prednisone for treatment of adult immune thrombocytopenia: a prospective multicenter randomized trial. *Blood* 2016; 127: 296–302.
 65. Cuker A, Neunert C. How I treat refractory immune thrombocytopenia. *Blood* 2016 [Epub ahead of print]
 66. Kühne T, Blanchette V, Buchanan GR et al. Splenectomy in children with idiopathic thrombocytopenic purpura: A prospective study of 134 children from the Intercontinental Childhood ITP Study Group. *Pediatr Blood Cancer* 2007; 49: 829–834.
 67. Aladjidi N, Santiago R, Pondarré C et al. Revisiting Splenectomy in Childhood Immune Thrombocytopenic Purpura in the Era of New Therapies: The French Experience. *J Blood Disorders Transf* 2012; S3: 003.
 68. Kojouri K, Vesely SK, Terrell DR, George JN. Splenectomy for adult patients with idiopathic thrombocytopenic purpura: a systematic review to assess long-term platelet count responses, prediction of response, and surgical complications. *Blood* 2004; 104: 2623–2634.
 69. Auger S, Duny Y, Rossi JF, Quittet P. Rituximab before splenectomy in adults with primary idiopathic thrombocytopenic purpura: a meta-analysis. *Br J Haematol* 2012; 158: 386–398.
 70. Wali YA, Al Lamki Z, Shah W et al. Pulsed high-dose dexamethasone therapy in children with chronic idiopathic thrombocytopenic purpura. *Pediatr Hematol Oncol* 2002; 19: 329–335.
 71. Khalafallah A, Rahman Z, Ogden K, Hannan T. Successful treatment with thrombopoietin receptor agonist in avoiding splenectomy for patients with chronic refractory immune thrombocytopenia. *Mediterr J Hematol Infect Dis* 2012; 4: e2012003.
 72. Schifferli A, Kühne T. Chronic immune thrombocytopenia in children: who needs splenectomy? *Semin Hematol* 2013; 50: S58S62.
 73. Kühne T. Treatment of pediatric primary immune thrombocytopenia with thrombopoietin receptor agonists. *Semin Hematol* 2015; 52: 25–30.
 74. Tarantino MD, Bussel JB, Blanchette VS et al. Romiplostim in children with immune thrombocytopenia: a phase 3, randomised, double-blind, placebo-controlled study. *Lancet* 2016; 388: 45–54.
 75. Neunert C, Despotovic J, Haley K et al. Thrombopoietin Receptor Agonist Use in Children: Data From the Pediatric ITP Consortium of North America ICON2 Study. *Pediatr Blood Cancer* 2016; 63: 1407–1413.
 76. Bussel JB, de Miguel PG, Despotovic JM et al. Eltrombopag for the treatment of children with persistent and chronic immune thrombocytopenia (PETIT): a randomised, multicentre, placebo-controlled study. *Lancet Hematol* 2015; 2: e315e325.
 77. Grainger JD, Locatelli F, Chotsampancharoen T et al. Eltrombopag for children with chronic immune thrombocytopenia (PETIT2): a randomised, multicentre, placebo-controlled trial. *Lancet* 2015; 386: 1649–1658.
 78. Kuter DJ, Bussel JB, Newland A et al. Long-term treatment with romiplostim in patients with chronic immune thrombocytopenia: safety and efficacy. *Br J Haematol* 2013; 161: 411–423.
 79. Saleh MN, Bussel JB, Cheng G et al. Safety and efficacy of eltrombopag for treatment of chronic immune thrombocytopenia: results of the long-term, open-label EXTEND study. *Blood* 2013; 121: 537–545.
 80. Cines DB, Gernsheimer T, Wasser J et al. Integrated analysis of long-term safety in patients with chronic immune thrombocytopenia (ITP) treated with the thrombopoietin (TPO) receptor agonist romiplostim. *Int J Hematol* 2015; 102: 259–270.
 81. Mahevas M, Fain O, Ebbo M et al. The temporary use of thrombopoietin-receptor agonists may induce a prolonged remission in adult chronic immune thrombocytopenia. Results of a French observational study. *Br J Haematol* 2014; 165: 865–869.
 82. Gonzalez-Lopez TJ, Pascual C, Alvarez-Roman MT et al. Successful discontinuation of eltrombopag after complete remission in patients with primary immune thrombocytopenia. *Am J Hematol* 2015; 90: E40–E43.
 83. Schifferli A, Kühne T. Thrombopoietin Receptor Agonists: A New Immune Modulatory Strategy in ITP? *Semin Hematol* 2016; 53: S31–S34.
 84. Kühne T, Freedman J, Semple JW et al. Platelet and immune responses to oral cyclic dexamethasone therapy in childhood chronic immune thrombocytopenic purpura. *J Pediatr* 1997; 130: 17–24.
 85. Borgna-Pignatti C, Rugolotto S, Nobili B et al. A trial of high-dose dexamethasone therapy for chronic idiopathic thrombocytopenic purpura in childhood. *J Pediatr* 1997; 130: 13–16.
 86. Khellaf M, Charles-Nelson A, Fain O et al. Safety and efficacy of rituximab in adult immune thrombocytopenia: results from a prospective registry including 248 patients. *Blood* 2014; 124: 3228–3236.
 87. Liang Y, Zhang L, Gao J et al. Rituximab for children with immune thrombocytopenia: a systematic review. *PLoS One* 2012; 7: e36698.
 88. Matsubara K, Takahashi Y, Hayakawa A et al. Long-term follow-up of children with refractory immune thrombocytopenia treated with rituximab. *Int J Hematol* 2014; 99: 429–436.
 89. Dai WJ, Zhang RR, Yang XC, Yuan YF. Efficacy of standard dose rituximab for refractory idiopathic thrombocytopenic purpura in children. *Eur Rev Med Pharmacol Sci* 2015; 19: 2379–2383.
 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.
 91. Choi PY, Roncolato F, Badoux X et al. A novel triple therapy for ITP using high-dose dexamethasone, low-dose rituximab, and cyclosporine (TT4). *Blood* 2015; 126: 500–503.
 92. Zhou H, Xu M, Qin P et al. A multicenter randomized open-label study of rituximab plus rITPO vs rituximab in corticosteroid-resistant or relapsed ITP. *Blood* 2015; 125: 1541–1547.
 93. European Medicine Agency. Revolade. http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/001110/human_med_001322.jsp&mid=WC0b01ac058001d124 (accessed October 1, 2016)