Immune thrombocytopenia (ITP) is a rare bleeding diathesis with a marked heterogeneous pathophysiology resulting in clinical variety and unpredictable treatment responses. Children often experience short courses of thrombocytopenia; however, persistent and chronic ITP occurs in 20–30% with a minority of children having therapy-refractory and severe ITP. Because of its rarity, clinical, and particularly academic, investigator-driven research is difficult to perform. High costs, a lack of manpower and increased administrative requirements are obstacles to progress. Such difficulties are recognized by the academic community and led to international coordination efforts to optimize the use of resources and to ensure high research standards. Consensus statements, practice guidelines and revisions have been well established, and may support the clinician with advice and recommendations based on evidence or consensus where evidence is lacking. Watchful waiting is now integrated into guidelines and new therapeutics are being investigated, and these have led to fruitful discussion and resulted in new potential pediatric strategies. Treatment end points other than the platelet count have been established and there are attempts to incorporate these into clinical practice. It has been suggested to introduce management strategies that can overcome the rigidity of practice guidelines. Last but not least, management recommendations must also provide space for patients to express their point of view.

Learning goals
At the conclusion of this activity, participants should be able to:
- understand the background of current definitions, diagnosis and treatment strategies in children with primary ITP;
- understand the significance of experience, consensus and evidence in pediatric primary ITP;
- be aware of the risks associated with watchful waiting, first- and second-line therapies and splenectomy;
- be aware of the clinical differences between children and adults.

Introduction
Immune thrombocytopenia (ITP) is an autoimmune-mediated acquired bleeding diathesis characterized by isolated thrombocytopenia (platelet count <100x10^9/L), with otherwise normal blood counts and leukocyte differential analysis in children with or without hemorrhagic diathesis who are healthy without signs and symptoms suggesting other diseases.\(^1\) In primary ITP, an underlying disorder or trigger is not identified, whereas secondary ITP refers to immune-mediated thrombocytopenia with known etiology, such as infectious diseases, e.g. HIV, helicobacter pylori, hepatitis C, and others, as presented in Table 1.\(^2\)

Pediatric ITP includes several age groups, each with their own characteristics, including infants, pre-school and school children, children at puberty, and adolescents.\(^3\) The differences between these groups consist in clinical characteristics, such as gender ratio, bleeding phenotype and quality of life, but also in characteristics of ITP, such as occurrence of bleeding (insidious or acute onset), presenting platelet count, incidence of co-morbidity, and number of persistent and chronic ITP events. Unfortunately, various obstacles have to be overcome and these make clinical research in children and adolescents difficult, complex and often costly. These are:
- the rarity of ITP;
- the number of different age groups each with different clinical characteristics;
- the fact that 70-80% of children have a self-limiting course of ITP, thus leaving children with persistent and chronic ITP as a minority;
- the fact that drug research often neglects pediatric populations;
- a lack of awareness of the disease on the part of many physicians.

Given the significant lack of clinical data, almost 20 years ago, an international group of hematologists founded the Intercontinental Cooperative ITP Study Group (ICIS) and opened registries in order to gather clinical and laboratory data and to establish networks and scientific platforms (www.itpbasel.ch).\(^4\) Additionally, there is a growing interest in childhood ITP resulting in the setting up of many national and international working groups. There are also plans for an international coordination of pediatric research and prac-
Definitions

The language of ITP was harmonized by the International Working Group (IWG) at the Vicenza Consensus Conference in 2007. Since there is a significant lack of clinical prospective data, retrospective studies and expert opinion reflect textbook knowledge. However, the definitions of diagnosis, therapy and long-term follow up and care of these patients were highly heterogeneous and, therefore, limited comparisons and analyses. The harmonization strategy and definitions established at the Vicenza conference are becoming more and more visible. It is recognized that an additional conference is needed for pediatric definitions.

Immune thrombocytopenia is defined according to the duration of thrombocytopenia. The first three months after the diagnosis define newly diagnosed ITP. In persistent ITP, thrombocytopenia lasts longer than three months but less than 12 months. This is based on observation of children who often achieve a remission, also after six months and even later. Chronic ITP defines patients with a thrombocytopenia lasting more than 12 months. Severity of ITP refers to clinically relevant bleeding symptoms and not solely to the platelet count. Bleeding is clinically relevant if a therapeutic intervention is needed to stop bleeding and if there is new bleeding after successful anti-hemorrhagic therapy, which again needs therapeutic intervention. In pediatrics, it became clear that children with newly diagnosed ITP with severe presenting thrombocytopenia do not necessarily need drug therapy. The most recent revised guidelines of the American Society of Hematology recommend watchful waiting in children with dry hemorrhage, i.e. skin bleeding without mucous membrane bleeding regardless of the platelet count. Whether to proceed and recommend watchful waiting for children with dry and wet bleeding needs prospective clinical trials and consensus. There is limited evidence that wet hemorrhage in children with newly diagnosed ITP bears a higher risk of life-threatening bleeding than dry hemorrhage. A clinically descriptive classification including symptomatic, oligo- and asymptomatic ITP, irrespective of the platelet count, may represent a further attempt to classify childhood ITP.

In adults, refractory ITP refers to patients who failed splenectomy and have severe ITP or who are at risk of bleeding and require therapy. In children, a consensus has still not been achieved. As young age represents a contraindication for splenectomy, and as it has not been clearly defined at what age splenectomy can be performed with an acceptable risk for infectious disorders comparable with that of adult patients, this procedure is inadequate to serve as a criterion for therapy refractoriness in children.

Epidemiology

Primary ITP is rare and occurs in approximately 3-5 per 100,000 children depending on age and gender. Boys and girls are equally affected; however, there is a prevalence of boys in younger age groups and a less clear preva-
lence of girls in older children. The peak age of childhood ITP is 1-6 years. The epidemiology of ITP with a first peak in infants and small children, and a slight but constant increase in adolescents and adults, suggests different pathophysiological mechanisms. The majority of children have primary ITP; secondary ITP is much more rare, but has not been well studied in children.

Pathophysiology

The knowledge of pathophysiology of ITP is important to understand the enormous and unpredictable clinical variation between patients with ITP, the different and unforeseeable treatment responses, and the fact that there are different forms of ITP, such as self-limited, persistent, and chronic ITP.

Historically, primary ITP included many patients with purpuric rash and thrombocytopenia. However, an increase in the knowledge of immune and inflammatory response mechanisms and genetics, as well as the availability of many laboratory tests including molecular biology, has resulted in the discovery of diseases mimicking “primary ITP”, and thus led to a reduction in the number of patients with primary ITP. One such example is autoimmune lymphoproliferative disease, which presents with autoimmune diseases (cytopenia), chronic non-malignant lymphoproliferation and secondary malignancies. It was first described in the 1990s and has been found to be an inherited disorder of abnormal apoptosis based on mutations in proteins mediating apoptotic pathways, such as Fas, and rarely Fas ligand or Caspase 10. The discovery of diseases mimicking ITP, and now called either secondary ITP or thrombocytopenia of non-immunological mechanisms, is growing (Table 1). The Pediatric and Adult Registry on Chronic ITP (PARC-ITP) is analyzing the ‘quality’ of diagnosis of patients with primary ITP prospectively and will report on patients changing their diagnosis to secondary ITP during their disease course.

Primary ITP is an immune-mediated bleeding disorder with premature platelet destruction by Fc receptor-mediated phagocytosis of the monocytic-phagocytic system mainly of spleen and liver and an impaired platelet production. Autoantibodies, most frequently of the IgG type, bind to platelet and megakaryocyte epitopes, mainly glycoproteins IIb-IIIa, Ib-IX, Ia-IIa, and result in an ineffective mega- and thrombopoiesis. Besides humoral abnormalities, there are also other mechanisms affecting platelets, including molecular mimicry, cellular abnormalities, oxidative stress and others.

The fact that there are patients with both self-limited and long-lasting ITP suggests different mechanisms. Children, but also adults, with a short course of thrombocytopenia and with therapy-induced or spontaneous recovery, have newly diagnosed or persistent ITP. In these patients, an infectious viral disorder can often be observed before thrombocytopenia. It is hypothesized that platelet proteins from the host may exhibit similarities of microbial proteins. Thus host immune responses against pathogenic antigens may cross-react against host proteins resulting in autoimmunity with inflammatory and destructive processes. This mechanism could be clearly demonstrated in children infected with varicella zoster virus. While infectious disease-associated immune reactions seem to be frequent pathomechanisms associated with childhood ITP, approximately one-third of children have the typical autoimmune disease observed in adults with long-lasting thrombocytopenia; therefore, the various mechanisms explained below may also be present in children. Although self-limited ITP suggests infectious diseases as etiological background, it is not well understood whether viruses are also capable of inducing immune dysregulation and subsequent chronic ITP, and this needs further investigations.

Meanwhile, it is well known that immune responses consist of complex humoral and cellular mechanisms. However, it is still unclear whether these mechanisms are causative in ITP or whether they are the result of inflammatory mechanisms associated with ITP. Imbalance between maintenance of peripheral T-cell tolerance and autoimmunity and of anti-inflammatory and pro-inflammatory mechanisms is well recognized. CD4+CD25+ Foxp3+ regulatory T cells regulate self-tolerance, suppress acquired immune responses and play an important role in autoimmune disorders.

Based on cytokine measurements, it has been recognized that patients with ITP, mainly the chronic form, have auto-reactive T cells with Th1 polarization characterized by interferon-gamma, and interleukin-2, which may result in autoreactive B-cell differentiation. Also Th17 cells may play a pathogenic role in ITP, although this has not been established so far. There is also another subtype of T-helper cells identified by their IL-22 and TNF-α cytokine secretion which are elevated in patients with primary ITP. Thus, ITP is associated with elevated T-cell-related pro-inflammatory cytokines. Moreover, it has been shown that cytotoxic T cells may directly destroy platelets and megakaryocytes. B-cell-activating factor (BAFF) and its homolog, a proliferation-inducing ligand (APRIL) belonging to the tumor necrosis factor superfamily, are potent cytokines and affect B-cell differentiation, maturation and survival, and may play a role in ITP, as dysregulation in these cytokines has been reported. A dysbalanced regulatory compartment may include B-regulatory cells (CD19+CD24+CD38- population) which mediate their regulatory function in part by IL-10.

Oxidative stress with overproduction of reactive oxygen species and deficient antioxidant defense mechanisms may also be responsible for platelet destruction. Furthermore, familial ITP has also been observed and suggests secondary ITP or thrombocytopenia due to other factors based on genetical involvement.

Clinical presentation

Children with newly diagnosed ITP often manifest with a dramatic spread of skin (dry) bleeding and sometimes also of mucous membrane (wet) bleeding within hours and days, with nose and gum bleeds and rarely hematuria or bloody stools. Also menorrhagia may be present. Wet bleeding has been associated with an increased risk for life-threatening bleeding requiring urgent treatment in contrast to dry bleeding; however, this observation is not evidence based. Intracranial hemorrhage (ICH) is rare and recent literature suggests that it occurs in less than 0.5% of children with newly diagnosed ITP. Retrospective data suggest that it is associated with a low platelet count.
of less than 20×10^9/L; however, there are not enough data based on prospective trials to define its occurrence and the risk factors. ICH can be observed at all phases of ITP and occurs also in treated patients.

Infections and vaccinations may be seen before the onset of ITP. The peak of these pediatric infectious disorders and that of pediatric ITP exhibit similar patterns.

Bleeding varies and is caused by thrombocytopenia and potentially by platelet dysfunction, and may also be affected by endogenous (e.g. congenital disturbances in the hemostatic system) and exogenous (e.g. drugs) factors. Bleeding may predict the outcome of children with ITP; it has been shown that an abrupt onset of bleeding is associated with resolution of ITP. Bleeding can be classified and expressed as bleeding scores. The IWG proposed a bleeding score, which probably needs adaptation for pediatric populations. Elaboration and validation of such bleeding scores are still complex, reflected by unawareness of the predictive value of bleeding, particularly life-threatening bleeding, the dynamics of occurrence of bleeding, and potential endogenous and exogenous factors affecting hemostasis. The usefulness of bleeding scores as bedside tests and the possibility of their use in clinical practice still has to be demonstrated.

Health-related quality of life has gained attention. Although this is difficult to assess and to interpret, there are growing reports of patient experience. However, quality of life measurements and assessment need to be further developed in the light of the greater evidence available. Self- or proxy-rated methods based on questionnaires are used. It has been demonstrated that the perspective of patients was neglected, that this often differs from that of physicians, and that patients' views must be included in the clinical decision-making process. Patients' well-being is uppermost in their own list of priorities and this may be seen independently of bleeding symptoms and platelet counts.

Diagnosis and differential diagnosis

The diagnosis of primary ITP is based on the clinical presentation and complete blood count including blood smear analysis. Bone marrow aspiration and biopsy is generally not needed, even when treating the patient with corticosteroids. However, if there are anamnestic, clinical signs, or symptoms not consistent with the diagnosis, or if there are any values not in the range of age-adjusted normality in the complete blood count, or any morphological abnormalities in the blood smear, further testing including bone marrow diagnostics must be considered. There is no laboratory test to confirm the diagnosis of primary ITP, thus it remains a diagnosis of exclusion. Differential diagnosis is presented in Table 1. A diagnostic algorithm for children with chronic ITP has not been elaborated.

Who needs treatment?

Main treatment goals of all phases of childhood ITP include improvement of quality of life, prevention and treatment of bleeding, emergency treatment for life-threatening bleeding, transient increase of platelets before surgical interventions or before sport activities, and attempts to defer splenectomy. It is the responsibility of the physician to interpret the platelet count, to translate it into a bleeding risk category and to inform the patient accordingly. The physician and the patient should be aware of the limits of the platelet count as surrogate indicator for bleeding risk. Unfortunately, these main goals of managing a child with ITP, particularly prevention of bleeding, are difficult to study through randomized clinical trials because of the rarity of ITP and of the large number of patients such trials require. Thus, the management of a child with primary ITP depends on the experience of the clinician, the existence of evidence or consensus where evidence is missing, availability of guidelines and the ability to interpret them while being aware of their limitations.

The reasons for using the platelet count as a treatment end point reflects experience with this parameter in clinical practice and research over a long period of time, its rapid availability as a bedside test and the absence of diagnostic tests capable of confirming ITP. Severe bleeding with ICH as its most feared form is often, but not always, associated with a low platelet count of less than 20×10^9/L. Clinicians should be aware of the technical problems associated with the platelet count, including the pre-analytical and analytical difficulties, particularly when thrombocytopenia is in the lower range. It is important to be aware of the fact that the bleeding phenotype does not depend solely on thrombocytopenia, but also on other factors such as age, co-morbidity, concomitant use of drugs, inherited disturbances of primary and secondary hemostasis, and anatomical malformations. A strict platelet count trigger for the management of patients with ITP does not represent the same situation in all cases, as has been seen in patients with bone marrow failure.

There is a substantial lack of evidence to help in the management of children with ITP, and this is reflected by consensus-based clinical practice guidelines. These guidelines may improve the clinical practice of physicians who are not experts, may standardize management, help provide comparable clinical data, and control costs. However, these guidelines also have their limitations: their rigidity; the fact that revision processes and their publication need time and create costs; the existence of multiple national and international guidelines; the fact that there is evidence of deviations from or non-adherence to guidelines.

These limitations have led to proposals for alternative management structures. Grace proposed “standardized clinical assessment and management plans” with active variance feedback loops to modify guidelines. Klaassen pointed to the need for shared decision making to include an exchange of information between families and their clinicians, and to use this information to contribute to patient-centered care. The increasing importance given to the viewpoint of patients is demonstrated by the growing number of patient organizations and this too may affect patient management.

Treatment options

The management of children with ITP is summarized in Figure 1 and includes watchful waiting (i.e. observation without drugs), first-line treatment, second-line treatment,
Figure 1. Management of children with ITP is based on the diagnosis of "primary ITP", which is distinguished from secondary ITP or thrombocytopenia due to other reasons by differential diagnostic considerations. Watchful waiting is chosen if the patient has no or mild bleeding irrespective of platelet count. If the physician decides on treatment, first-line treatment is indicated. Treatment indication is based on individual factors: additional bleeding risk factors, quality of life aspects, fear of life-threatening bleeding by patient and/or parents, and wish for preventive drug treatment. Second-line treatment is indicated in children with persistent and chronic ITP who are not responding to first-line treatment, and who have bleeding and low platelet counts. The decision to administer second-line treatment is highly individual. Splenectomy cannot be generally recommended for children (morbidity and rarely mortality). The younger the child, the stronger are the arguments against splenectomy; therefore, splenectomy does not have the strategic role it has in adult ITP. (Platelet count)*: not needed for the decision of watchful waiting; Tcpenia: thrombocytopenia.
and splenectomy. First- and second-line treatments may be considered for children with ITP during all phases of ITP. Second-line treatment does not imply that first-line treatment should no longer be used; thus the terms “first-line” and “second-line” used in oncology are somewhat inadequate for patients with autoimmune disorders. Treatment options have been described in detail in current practice guidelines and reviews and are presented in Tables 2 and 3. Watchful waiting is now an accepted management procedure for children with no or mild skin bleeding, and is mentioned in the most recent practice guidelines. This option is often associated with lengthy and time-consuming dialogue with patients and their parents, and depends on the experience of the physician. Its advantages include prevention of drug escalation, avoidance of adverse side-effects and of the terror caused by repeated check-ups to test platelet counts.

The clinical and strategic significance of the platelet count loses its weight in children with persistent and chronic ITP. Generally these patients are treated according to bleeding and quality of life. Chronic ITP in children is a poorly investigated area and not well covered by practice guidelines, and needs further clinical research and consensus. Watchful waiting is indicated in children with no or mild bleeding, and first-line therapy may be considered in children with moderate and severe bleeding and in those with a poor quality of life. Adverse drug effects are frequent and can be devastating in patients under long-term therapy. Thus, avoiding adverse drug effects represents an important treatment goal in children with persistent and chronic ITP. Immuno- globulins and corticosteroids should be considered particularly in those children who previously responded well. In pediatrics, second-line therapies are not well established, are not licensed and are usually indicated on the basis of individual factors. The drugs that are currently the focus of attention for adult patients are also under investigation in children. These include rituximab, thrombopoietin receptor agonists, and immunosuppressants. In a systematic review of rituximab in studies of at least 5 children, it was concluded that rituximab is effective in primary and secondary pediatric ITP, that the safety profile of this drug is acceptable, but that clinical randomized and controlled trials are urgently needed. In a phase I/II study, 22 children were enrolled and randomly assigned to placebo (n=5) and romiplostim (n=17) for 12 weeks. Children with a duration of thrombocytopenia of six months or over were stratified by age. Effects were similar to those seen in adults, with platelet counts of 50×10^9/L or over for two consecutive weeks being achieved by 15 of 17 patients treated with romiplostim and by none treated with placebo. The adverse event profile was also similar to that observed in adults with no serious treatment-related adverse events. Long-term safety issues, including bone marrow fibrosis, have not yet been investigated in children. Recently, a single-center study was reported in 66 adults on various thrombopoietin-receptor agonists with a median treatment duration of 29 months. Bone marrow fibrosis of grades 2/3 was found in approximately one-fifth of patients and it seems that fibrosis may progress in these patients, although its clinical significance remains unclear and should be investigated in further studies. Among immunosuppressants, mycophenolate mofetil exhibited promising results, and although sirolimus has not been well investigated, it seems to be a drug with a potential for long-term use and a favorable safety profile. The rarity of ITP, and the rarity of chronic symptomatic ITP in children, makes it difficult to study second-line treatments. A close collaboration with hematologists dealing with adult ITP and a careful interpretation of study results is advisable. In such collaborative processes, hematologists should be aware that extrapolation of experience and data from adult into pediatric hematology is not feasible without a critical assessment capable of identifying gaps in knowledge that need to provide the focus for pediatric-specific studies.

**Table 2. Standard (“first-line”) therapy of children with primary immune thrombocytopenia.**

<table>
<thead>
<tr>
<th>Therapeutic class</th>
<th>Drug*</th>
<th>Route</th>
<th>Recommended dose*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Corticosteroids</td>
<td>Prednisone Methylprednisolone</td>
<td>Oral Intravenous</td>
<td>2 mg/kg/day for 14 days then tapering 4 mg/kg/day for 4 days without tapering 30 mg/kg, max. dose 1000 mg/day for 3 days</td>
</tr>
<tr>
<td>Immunoglobulins</td>
<td>Intravenous</td>
<td></td>
<td>0.8 g/kg for 1-2 days</td>
</tr>
<tr>
<td>Immunoglobulins</td>
<td>Anti-D</td>
<td>Intravenous</td>
<td>75 microg/kg for 1 day</td>
</tr>
</tbody>
</table>

*There are other dose recommendations.

**Table 3. Second-line therapy of children with primary immune thrombocytopenia.**

<table>
<thead>
<tr>
<th>Therapeutic class</th>
<th>Drug*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Splenectomy</td>
<td>Anti-CD 20 (rituximab)* Anti-CD 52 (alemtuzumab)</td>
</tr>
<tr>
<td>Monoclonal antibodies</td>
<td>Romiplostim* Eltrombog*</td>
</tr>
<tr>
<td>Monoclonal antibodies</td>
<td>Arathiopine Cyclophosphamide Cyclosporin A* Mycophenolate mofetil Sirolimus Etanercept</td>
</tr>
<tr>
<td>Immunosuppressants</td>
<td>Cytostatic drugs</td>
</tr>
<tr>
<td>Antibiotics</td>
<td>Danazol</td>
</tr>
<tr>
<td>Antibiotics against H. pylori*</td>
<td></td>
</tr>
<tr>
<td>Miscellaneous</td>
<td>Dapson* Anti-CD40 ligand inhibitors Syk inhibitors</td>
</tr>
</tbody>
</table>

*List of drugs not licensed for pediatric use that have been investigated at least in part in pediatric patients with ITP.*
has been poorly investigated. Furthermore, the pre-, peri- and postoperative management is not standardized. Although splenectomy is effective, disadvantages and complications must be weighed against its possible benefits. Current guidelines include splenectomy that should not be used in young children because of an increased risk for fatal infectious complications with encapsulated bacteria. Patients must be instructed that splenectomy is associated with various health-related issues, such as vaccinations against encapsulated bacteria, antibiotic prophylaxis after the procedure, planning and organizing medical assistance while traveling, regular clinical visits, and carrying relevant medical information on their person. Furthermore, splenectomy may result in surgical complications and poor or non-response, and does not guarantee freedom from relapse of ITP. The spontaneous improvement, and sometimes normalization, of bleeding and thrombocytopenia is a feature of ITP and an important argument against splenectomy in children. In adults, strategies to defer splenectomy have been published, including use of rituximab and dexamethasone and, more recently, thrombopoietin mimetics. Such strategies may also be considered in children.

Treatment of children with life-threatening bleeding has not been rigorously investigated, but there is consensus as to how to treat children in these situations. A combination of platelet transfusions, intravenous high-dose corticosteroids and intravenous immunoglobulins are used. Life-threatening bleeding represents the only clear indication for platelet transfusions. These therapies may be repeated according to the clinical situation. Emergency splenectomy has been performed successfully but cannot be recommended based on the evidence available. Experience with activated Factor VII in such situations remains limited.

Outlook

Coordination of clinical research and careful use of the limited resources available are crucial for progress to be made. Groups such as the IWG and the ICIS group are already active on the international stage, and a pediatric consensus initiative similar to that of the IWG is currently under evaluation. A generally accepted diagnostic algorithm for children with persistent and chronic ITP is warranted. Furthermore, randomized clinical trials are needed to optimize the management of children with persistent and chronic ITP. These international activities may benefit from including the views of the patients and their caregivers.

References