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Advanced concepts of Childhood Immune Thrombocytopenia

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ABSTRACT

Pediatric immune thrombocytopenia (ITP) is a heterogeneous autoimmune condition with variability in etiology, bleeding phenotype, need for treatment and response to therapy, as well as duration of disease. Fortunately, many children have mild bleeding and experience spontaneous disease resolution, however it is not possible to predict which patients will have this outcome. For most children, initial management involves attention to screening for underlying secondary causes of ITP, followed by careful observation. When treatment is required, first line therapies are relatively standardized and aim to rapidly diminish bleeding risk. When ITP becomes persistent, chronic or otherwise necessitates alternative therapies, there is much less existing data on the optimal sequence of treatment choices and hence more variability in clinical practice. Further complicating management, there is no reliable way to predict which treatments will be effective, leading patients to be exposed to adverse effects of therapy without confidence in the degree of response. ITP management continues to evolve: as research expands our understanding of the molecular underpinnings of ITP, providers are increasingly able to refine and individualize treatment regimens. Further, novel therapeutics are being tested and used to treat adult ITP patients and these drugs may ultimately be applied to the benefit of children with this condition

Keywords: immune thrombocytopenia, pediatrics, plate-lets, management

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 [(1)].

Pediatric ITP includes several age groups, each with their own characteristics, including infants, pre-school and school children, children at puberty, and adolescents. 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 [(2)].

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 5 and even later [(3)]. 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 [(4)].

There are three forms of ITP based on the duration of thrombocytopenia [(5)]:

1. **newly diagnosed ITP** (first 3 months): "Acute ITP" should not be used any- more, 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 re- flects the appreciation of the high po- tential of improvement of ITP during the first year after diagnosis.
3. **chronic ITP** (> 12 months)

Severe ITP is defined by the presence of bleeding symptoms at presentation suffi- cient to mandate treatment, or occurrence of new bleeding symptoms during the course, requiring additional therapeutic in- tervention with a different platelet-enhan- cing agent or an increased dose[(6)].

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 re- garding refractory ITP could not yet be achieved, because

- splenectomy is contraindicated in young children and
- a clear definition at which age a splenec- tomy can be performed with a balanced risk for overwhelming infectious diseases is absent[(6)].

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 [(7)]. Interestingly, in infants – and less frequently in young children – ITP occurs more often in boys. The reasons therefore are unknown. 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. ITP exhibits a first peak between the age of 1 and 6 years. 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 [(8)].

Pathophysiology andPathogenesis

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 under- stood, as well as how appropriate treatments should be directed to restore physio- logical immunocompetence [(8)].

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[(10)].

T-cells play an important role both in auto- antibody 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 inter- feron-gamma) can be typically seen. Additionally, it has been shown that CD8+ T-cells are capable to lyse autologous platelets *in vitro*, which has been demonstrated by other groups [(11)]. Immune dysregulation, resulting in T- and B-regulatory cell disturbances, plays also an impor- tant role. There is evidence indicating that some specific immune cells may induce autoimmune diseases, such as[(12)]:

- Th17,
- Th22 and
- T-follicular helper cells

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. Recently, it has been shown that occult bleeding is more frequent than anticipated. 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 infec- tions interfering with haemostasis) [(13)].

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[(14)].

The platelet count of children with ITP at first presentation is less than 20 × 109 / l in approximately 80 %. Nonetheless, major haemorrhage is rare – also in its broad definition, that has been used by the Inter-continental Childhood ITP Study Group (ICIS) Registry II, such as intra-cranial or other overt internal or mucous membrane bleeding, which results in anaemia or requires local treatment to stop haemorrhage[(15)].

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. These infections occur at the same peak age as ITP does[(16)].

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 [(17)].

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 in itial diagnosis,
- 16 % between 6 and 12 months and
- 24 % between 12 and 24 months [18].

In registries the percentage of children with chronic ITP is approximately 30 %. How- ever, 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

  $< 20 \times 1^{09}$ / l was present [19].

This high remission rate was also demonstrated in a Korean cohort [20].

Diagnosis and differential diagnosis

Primary ITP is a diagnosis of exclusion. A threshold platelet count of less than 100×1^{09}/l was established by the IWG based on the observation that individuals with a platelet count of 100–150 × ^{109}/l have a low probability of developing severe thrombocytopenia, and that platelet values of 100–150 × 1^{09}/l are frequently found in individuals of non-Western origin [21].

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.
- Family history is usually negative regarding bleeding disorders. If positive, differential diagnostic considerations should be undertaken, which is de- scribed elsewhere.
- Physical examination does not reveal any abnormalities except haemorrhagic diathesis consisting of petechiae and subcutaneous hematomas, and some- times 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[22].

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. Bleeding as a treatment endpoint has the potential to change therapeutic requirements [23].

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 bleed- ing disorders or oncology, the develop- ment and validation of tools to measure HR-QoL are complex and challenging and still far away from clinical practice. Pediatric tools specific to ITP were developed and practiced in clinical trials [24].

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[25]. In contrast to children with newly diagnosed ITP, the degree of evidence is low for recommendations in children with persistent and particularly chronic ITP[26].

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 (30 mg/ kg for 3 days).

In other situations platelet transfusions are not indicated.

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

There is limited experience for recombinant factor VIIa, also in combination with fibrinogen [(27)].

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 [(28)] were the first ones that clearly recom- mended watchful waiting for children with no or mild bleeding. Former guidelines de- fined such mild bleeding as skin manifes- tations only (e. g. bruising or petechiae), and stated that treatment decision could be made regardless of the platelet count [(29)].

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 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 [(30)].

Second-line treatment is rarely needed in children with newly diagnosed ITP. It is indicated in symptomatic children that are not responding to first-line treatment [(1)].

Persistent ITP

This category of ITP has been created to point out the high potential of patients with ITP who will improve or recover with- in 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 [(31)].

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. 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. Because of the fact that chronic symptomatic ITP is that rare it is extremely hard to generate evidence-based data [(32)].

Splenectomy

Although splenectomy is an effective treatment in children and has the potential to cure the patient, it has not the same strategical significance as for adults [(33)]. 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 [(21)].

In children splenectomy is associated with an increased risk for overwhelming infections by encapsulated bacteria, such as[(34)]:

- 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. [(35)]:

- 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 [36].

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 [37].

Second-line therapy

Second-line therapy is rarely used in children. Thrombopoietin receptor agonists (TPO-RAs) are successful drugs in adults and are also studied in children [38]. 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 [39]. There is increasing knowledge of long- term safety in adults but not in children. Potential and theoretical risks include [40]:

- 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 hae- matopoietic stem cell depletion.

Long-term safety of TPO-RAs is an important area of future pediatric clinical re- search. Sustained response after stopping TPO-RAs in adults has been observed and will be studied. Other second-line therapies include[41]:

- 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. Adverse effects of dexamethasone can be substantial [42].

Rituximab has been studied in adult patients successfully with an acceptable safety profile that could be reproduced in children. However,

there are no comparative studies and experience of this drug for children is still limited [(1)].

Addition of dexamethasone to rituximab has been shown to increase the effect [(43)]. Combination therapies of rituximab, dexame- thasone 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. However these regimens are reserved for most severely affected patients and may be toxic, thus their benefit must be carefully weighed against their risks [(44)].

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 [(1)].

Alternative treatments

After first- and second-line therapies have been tried, the next therapy option is selected in discussions between the medical team, caregivers and patient. In a study focused on treatment choices from the ITP Consortium of North America, the most common reason to select a particular agent was the possibility of long-term remission, followed by parental or patient preference, and side effect profile [(45)]. Other factors which impact decision making include the provider's experience and ease of administration for the individual drugs [(46)].

There is a paucity of large, formal studies evaluating outcomes of third line agents in pediatric ITP and certainly, there are no randomized controlled trials comparing the many available therapies directly. Other agents used as third line management include purine analogues (azathioprine, mercaptopurine), mycophenolate mofetil, sirolimus, cyclophosphamide, cyclosporine A, dapsone, danazol and vincristine. Collectively, initial response rates for these drugs range from around 30–60% [(47)].

Conclusion

For many children ITP symptoms are mild and self-resolve, and it would initially seem that treatment is straight forward. However, pediatric ITP is a heterogeneous disorder, with each patient's case differing in

bleeding phenotype, duration of disease and response to therapy. In particular, for those with chronic ITP, multi-lineage cytopenias or individuals with thrombocytopenia which is a component of another underlying systemic disorder, management is even more complex. The field of ITP study continues to identify more genetic risk factors. These can now be leveraged to both elucidate the cause of an individual child's ITP, and be used to develop better targeted therapies in the future.

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