

REVIEW PAPER

Immune thrombocytopaenia in children and adolescents – current management and Polish perspective

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ABSTRACT

Immune thrombocytopaenia (ITP) is the most common cause of acquired thrombocytopaenia diagnosed in paediatric patients. It is described as an isolated thrombocytopaenia without other factors, which may cause a decrease in platelets. Therefore, the diagnosis is of exclusion. Over the last few years, its management has significantly developed, and a paradigm switch in second-line treatment is being observed. Currently, thrombopoietin receptor agonists (TPO-RA) are available in Poland, which reduce the need for splenectomy in affected patients. The use of thrombopoietin receptor agonists has also provoked a change in definitions, especially concerning refractory ITP. This review focuses on an overview of currently recommended diagnostics and treatment of ITP, ongoing research concerning genetic predisposition, the use of TPO-RA, other immunosuppressive agents, and the role of splenectomy. We summarise congenital thrombocytopaenic disorders, which are the most often mistaken as ITP and need to be considered in the differential diagnosis.

KEY WORDS:

immune thrombocytopaenia, thrombopoietin receptor agonists, splenectomy.

INTRODUCTION

Immune thrombocytopenia (ITP), formerly known as primary ITP or Werlhof disease, is an acquired autoimmune disease leading to isolated thrombocytopaenia and frequent bleeding, ecchymoses, and petechiae [1]. It is defined by isolated thrombocytopaenia, i.e. $< 100 \times 10^9/l$ when no other factors that could induce low platelet levels are identified, being a diagnosis of exclusion [2]. The prevalence in the paediatric population is estimated as 2–5/100,000, but no specific epidemiological data has been collected in Poland to date [3]. Affected children are usually < 10 years old. Usually, the diagnosis is of exclusion of other causes of thrombocytopaenia [3]. The typical treatment consists of immunoglobulins intravenously or steroids. Second-line therapy includes thrombopoietin receptor agonists, romiplostim and el-

trombopag, which switched the role of splenectomy to a third- or further-line therapy. In refractory ITP, immunosuppressants such as rituximab might be considered [1]. Table 1 presents the definitions concerning ITP and the phases of the disease based on its length and response to the treatment. Notably, these definitions are variable between subsequent articles and guidelines, augmented by the advent of thrombopoietin receptor agonists (TPO-RA), which has immensely changed this disease's perspective and management [4, 5].

PATHOMECHANISM

Immune thrombocytopaenia is connected with platelet damage and impaired production [6]. The primary, and possibly the most common, pathomechanism concerns the dysregulation of immune equilibrium: regu-

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TABLE 1. Table shows the definitions of immune thrombocytopaenia that appear most frequently in the literature

Term	Definition
Newly diagnosed ITP (ndITP)	From diagnosis up to 3 months
Persistent ITP (pITP)	Disease lasting 3–12 months
Chronic ITP (cITP)	Duration longer than 12 months
Refractory ITP (rITP) (classic definition) [4]	Severe ITP with high risk of bleeding, refractory to splenectomy, requiring further treatment
Newly diagnosed refractory ITP [5]	ITP requiring treatment, did not respond to at least 2 first-line treatments at standard doses ($PLT < 20 \times 10^9/l$ at least one week after treatment)
Persistent/chronic refractory ITP [5]	ITP not responding to at least 2 second-line medications from different classes, independently of response to first-line treatment
ITP resolution [3]	Achieving a platelet count $> 150 \times 10^9/l$ on 2 occasions or one occasion in the presence of normalised MPV value, with no therapy used

ITP – immune thrombocytopaenia, MPV – mean platelet volume, PLT – platelet(s)

latory T-lymphocytes are lowered, while helper T-lymphocytes (Th17) are increased, resulting in immune disproportion and a higher Th1/Th2 ratio [7]. Such an imbalance leads to the activation of cytotoxic T-lymphocytes, followed by activation of autoreactive B-lymphocytes producing plasma cells and autoantibodies usually targeted on glycoprotein IIb/IIIa found on platelets. Opsonised platelets are caught by splenic macrophages using the Fcγ receptor [8]. This, in turn, leads to a vicious cycle of T-lymphocytes and B-lymphocytes activation, further damaging platelets. These platelets possess a bound fraction of thrombopoietin (TPO), and when destroyed, the TPO is lost, which results in counterintuitive normal or lowered levels of TPO in cITP, but also serves as a rationale for TPO-RA use [9]. Moreover, Fcγ receptor is also present on megakaryocytes, which can be damaged; hence, megakaryocytes are ineligible to produce thrombocytes or impaired cells. Autoantibodies might also be targeted against Ib glycoprotein on the platelets, which is rarer. This receptor is rich in sialic acid, and its targeting depletes sialic acid content, leading to further damage by hepatic macrophages – Kupffer cells [7, 10, 11]. Another pathomechanism is based on the complement activation and damage and destruction of the thrombocytes [12].

PREDISPOSITION TO IMMUNE THROMBOCYTOPENIA

A viral infection usually precedes ITP onset. There are ongoing studies on the role of genetic predisposition and ITP, especially in developing rITP or cITP. FcγR polymorphisms are one of the most often analysed, and they have already been associated with other diseases manifesting with thrombocytopaenia, such as heparin-induced thrombocytopaenia and systemic lupus erythematosus. They may cause a change in the receptor binding to IgG, triggering an immune response [13]. Not only are they found more often in patients with ITP, but they also might be considered prognostic factors. FCGR2C*ORF and FCGR2A*27W and the FCGR2B pro-

moter variants 2B.4 and FCGR2C*ORF are found more often in transient ITP patients but not in chronic subsets. On the other hand, deletion of *FCGR2C/FCGR3B* (copy number region 1) is correlated with chronic ITP [14]. The onset of symptoms is correlated with specific polymorphisms as well. For instance, *FCGR2A* H131R polymorphism occurs more frequently in childhood ITP [15]. Other polymorphisms that are investigated include the protein tyrosine phosphatase non-receptor 22 gene (*PTPN22*), which regulates signal transduction through the T-cell receptors and single nucleotide variants taking part in the Wnt/β-catenin signalling [16, 17]. This pathway is involved in the regulation of immune cell populations. Polymorphisms, which affect interleukins, are also associated with ITP. Increased levels of IL-23 and IL-17A were found in patients with ITP [18]. Interleukin-17F rs763780 (7488A/G) polymorphism was associated with greater susceptibility and severity of the disease [19]. Furthermore, the expression of specific genes may be used as a prognostic factor. Increased *GAS5* levels and decreased *RUNX1* are good prognostic factors, suggesting quicker recovery [20]. Given the heterogeneity of ITP, it is highly likely that there are many other genetic factors involved in the development of the disease.

DIAGNOSTICS

A typical paediatric patient suffering from ITP presents with new-onset severe thrombocytopaenia without earlier evidence of lowered platelet level or any other haematological abnormalities. They may not present with bleeding; however, petechiae, ecchymoses, mucosal bleeding, and epistaxis are the most frequent presentations of thrombocytopaenic purpura. Intracranial, intramuscular haemorrhages or hemarthrosis are the least expected. Another leading symptom is fatigue [1, 3]. Adequate diagnostics is crucial, given that ITP is a diagnosis of exclusion. However, according to the guidelines, only a complete blood count and peripheral blood smear are necessary for a ndITP with a typical clinical history,

negative familial background, and no other anomalies in the examination [1]. Clinicians need to carefully seek the presence of dysmorphic features, possible lymphadenopathy, hepatosplenomegaly, and take anamnesis regarding used medications. The immature platelet fraction and mean platelet volume (MPV) are often elevated in ITP, but MPV may not be reliable in severe thrombocytopaenia (platelet (PLT) level $< 10 \times 10^9/l$) [3, 21]. The baseline immunoglobulin panel (IgM, IgG, IgA) and their levels are often helpful, especially if the child had them done approximately 3 months before the onset of ITP, which is a rare scenario. This may be useful in predicting ITP chronicity – aberrant IgG levels (both low and high) were associated with cITP [22]. A positive direct antiglobulin test may be associated with a chronic disease and a need for second-line therapy [23]. The scope of viral and bacterial testing varies between countries. The most conflicting is testing for *Helicobacter pylori* in children, which should be done in the case of cITP. ESPGHAN/NASPGHAN guidelines support this approach, but only noninvasive testing is endorsed for possible asymptomatic infection [24]. The guidelines do not support viral and bacterial testing, but it is often done in practice.

Antiplatelet antibodies are not routinely detected, but IgM antiplatelet antibodies are positive in 62% of ndITP patients, while IgG only in 10%. These tests have little practical value [3]. Bone marrow biopsy should be performed in any doubtful case when malignancy or genetic background is possible; however, American Society of Hematology guidelines do not recommend routine biopsy in patients who do not respond to intravenous immunoglobulins [1]. Moreover, in chronic/refractory ITP, the diagnosis needs to be reevaluated, and rarer causes of thrombocytopaenia should be excluded. These include primary immune deficiency disorder, primary immune regulatory disease, and other genetic diseases, including inborn bone marrow failure [3]. At this point, secondary ITP needs to be considered as well. It may be divided into 3 groups:

- ITP secondary to autoimmune diseases: 7–10% of ITP cases,
- ITP secondary to infectious agents: hepatitis C: +/- 2% and human immunodeficiency virus: +/- 1%,
- ITP secondary to lymphoproliferative disorders (2–5%) [25].

Autoimmune diseases include systemic lupus erythematosus, antiphospholipid antibody syndrome, autoimmune thyroid disease, and Evans syndrome. Infectious agents provoking thrombocytopaenia consist of a vast group, including *Helicobacter pylori*, *Haemophilus influenzae B*, varicella zoster virus, hepatitis B and C virus (HBV and HCV), human immunodeficiency virus (HIV), cytomegalovirus (CMV), rubella, Epstein-Barr virus (EBV), and SARS-CoV-2, among others. Also, vaccinations, most commonly MMR (measles, mumps, rubella), can trigger ITP [26]. Testing for CMV, EBV, HBV, HCV,

HIV, and *Helicobacter pylori* is recommended in the case of chronic/refractory ITP, along with testing for autoimmune diseases and thyroid function [1].

IMMUNE THROMBOCYTOPAENIA TREATMENT

Immune thrombocytopaenia treatment initiation does not rely only on the patient's platelet count but rather on the child's clinical state. Bleeding scores have been developed to separate patients needing urgent care from patients able to be supervised in a watch-and-wait strategy.

The available bleeding scores are predominantly based on the clinical assessment. According to the authors of a current American consensus, grades 1–4 are named, and patients with grade 1–2 bleedings may be observed. Grade 1 concerns patients exhibiting minor bleeding, with < 100 petechiae and/or < 5 small bruises, with no mucosal bleeding. In grade 2 (mild) bleeding, the patient may present with > 100 petechiae and/or > 5 large bruises, defined as having more than 3 cm in diameter, but with no mucosal bleeding. Management should be undertaken in the case of grade 3 bleeding, defined as moderate, where clinically mucosal bleeding is active and/or the patient exhibits an active life, which could provoke more dangerous events. The patient should be at least hospitalised and thoroughly screened to start ITP treatment. This is usually the case for paediatric patients. In grade 4, a strict intervention is advised, as severe bleeding may be observed, and the patient suffers from acute and life-threatening anaemia or has a suspected internal haemorrhage. An indication of the treatment is also an abrupt change of behaviour or a necessity to use anticoagulants or non-steroid antiinflammatory drugs. Moreover, the familial situation (accessibility to healthcare, distance from the hospital, social status) should be of concern in further decision-making [1].

CORTICOSTEROIDS

Corticosteroids are available first-line therapy option. The standard predniso(lo)ne dose is 4 mg/kg/day *per dose* in 3–4 doses, given for 4 subsequent days. The maximum dose of predniso(lo)ne differs according to the source, either 120 mg/day or 200 mg/day. Such management requires no taper. Another proposed dose is 2 mg/kg on day 1, with a maximum dose of 80 mg/day, administered every day for 1–2 weeks [1, 3]. Alternatively, dexamethasone may be used 0.6 mg/kg/day *per os* (max. 40 mg/day) or 26 mg/m², or methylprednisolone 0.3–1.0 g/kg/day [3]. It is recommended to avoid administration longer than a week due to potential adverse effects, both short- and long-term, including secondary adrenal insufficiency, if they are not tapered after prolonged use. Such treatment should only maintain an acceptable platelet level, allowing for proper haemostasis. Corticosteroid treatment should yield a platelet increase within 2 weeks; if such improve-

ment is seen, steroids should be tapered before 3 weeks, despite an expected decrease in thrombocyte level [1]. The response rate can be higher than 95%, as reported by some studies, while others report 70–80% initial response within a maximum of 7 days of administration [1].

INTRAVENOUS IMMUNOGLOBULINS

The first-line therapy consists of intravenous immunoglobulins 0.4 g/kg/day for 5 consecutive days or a single dose of 0.8–1 g/kg at 1 or 2 successive days [1, 3]. The response rate reached above 80% [1, 27]. Sometimes paediatric patients react with an unspecified allergic reaction or headache, nausea, and vomiting to intravenous immunoglobulin – a recent study has shown that premedication with hydrocortisone augments the risk of such side effects and further medical assistance, including hospitalisation and imaging diagnostics, as compared to other premedication protocols, e.g. with paracetamol. Still, steroid premedication is indicated [1].

ANTI-D IMMUNOGLOBULIN

The Food and Drug Administration approves anti-D immunoglobulin to treat ITP, but such treatment is currently unavailable in Europe. The standard dose is 50–75 µg/kg intravenously, yielding similar response rates as corticosteroids or intravenous immunoglobulins (70–80%). Side effects may include haemolysis [1]. Given its unavailability, this review will not discuss its administration further.

THROMBOPOIETIN RECEPTOR AGONISTS

Two TPO-RAs are currently available within the drug program B.98 (treatment of idiopathic thrombocytopenia in paediatric patients) in Poland: romiplostim and eltrombopag. Both serve as the second-line therapy, and there are no strict guidelines on which medication should be administered as the first in the second-line setting [28]. The decision is based on the physician's, parents', and patient's opinions and adjustments. There is currently no data on the superiority of any of these pharmaceuticals. Importantly, in the case of an unsatisfactory response to one of them, it is possible to change the treatment to another, or they can be combined with mycophenolate mofetil [1]. The main inclusion criteria in the B.98 programme involve the age between 1 and 18 years and the diagnosis of cITP or ITP lasting at least > 6 months with no satisfactory response to prior first-line treatment. Importantly, a trephine biopsy is no longer obligatory before starting the treatment to exclude fibrotic changes in bone marrow. If the patient reaches 18 years of age, they may continue the treatment following the protocol for adults (B.97). In terms of side effects, TPO-RAs are generally safe drugs, with the most problematic being throm-

boembolic events; however, they seem to be less frequent than in adults [28]. Thrombopoietin receptor agonists should be tapered after 6–12 months of satisfactory, stable response with a view to discontinuation [1]. Usually, their weaning allows for thrombocyte level maintenance, especially in children who had them administered before 12 months of ITP duration [29, 30].

ROMIPLOSTIM

This is a subcutaneous medication the dosing of which relies on the patient's body mass (1 µg/kg) administered once weekly. Then, the dose is adjusted based on regular platelet count checkups and the patient's body weight to reach a platelet level $\geq 50 \times 10^9/l$. From a practical point of view, it may pose problems, as per its parenteral administration and a necessity to dissolve it prior to its use. Importantly, it does not have any interactions with food or drugs. If there is no response within 4 weeks of the treatment at the maximum dose (10 µg/kg), the patient is excluded from romiplostim administration.

ELTROMBOPAG

Eltrombopag is another TPO-RA available in the B.98 program; however, this substance is available in tablet form. This allows for less traumatic administration but may be ineffective in the youngest. The starting dose is 25 mg/day (at ages 1–5 years) and 50 mg/day (from 6 years of age), and the maximum dose is 75 mg/day. It should be ingested once daily. Notably, this drug has multiple interactions with food and other medications, e.g. it interferes with calcium, iron, magnesium, aluminium, selenium, and zinc-rich food, decreasing absorption [31]. Moreover, concurrent treatment with statins, methotrexate, and lopinavir/ritonavir should be omitted [32]. The inclusion and exclusion criteria are shared with romiplostim. Moreover, eltrombopag has been found to be effective in the treatment of post-allogeneic haematopoietic stem cell transplantation (allo-HSCT) thrombocytopenia at a starting dose of 50 mg/day or maintenance dose of 4 mg/kg/day [33].

AVATROMBOPAG

Although avatrombopag is not reimbursed or even available in Poland, it is a promising second-generation TPO-RA, increasing bone marrow platelet production. The starting dose is reported to depend on the age, for < 6-year-olds being 10 mg/day, and for > 6-year-olds – 20 mg/day [34]. Single studies assessing the response rates in heavily pretreated paediatric patients with cITP show promising results in switching from eltrombopag to avatrombopag [35]. One study reported the overall response and complete response as 81.8% and 54.6%, respectively,

but the study was executed on a small cohort of patients [35]. Adults report greater satisfaction while being treated with this medication, compared to eltrombopag/romiplostim, which may be due to a lack of food-drug interactions and oral administration but also to its overall effectiveness and fewer side effects [36]. Avatrombopag was also researched and proved effective in managing thrombocytopaenia after allo-HSCT, alleviating thrombocytopaenia and promoting engraftment [37].

HETROMBOPAG

Despite the current unavailability of such treatment in paediatric patients, there is an ongoing phase 3 clinical trial comparing this treatment to placebo (NCT04737850) for patients between 6 and 17 years of age, for 2 different time periods (8 and 24 weeks) [38]. Moreover, its activity in combination with an anti-CD20 antibody – rituximab or ortuzumab – is being assessed (NCT05718856), but hetrombopag is one of the possible TPO-RAs used in this phase 4 trial at doses varying according to the age of the patient – for 6–11-years-old – 3.75 mg/day and 12–17-years-olds – 5 mg/day [39].

OTHER THERAPIES

IMMUNOSUPPRESSIVE AGENTS: RITUXIMAB AND MYCOPHENOLATE MOFETIL

Rituximab, an anti-CD20 monoclonal antibody, may be used in rITP in the paediatric population. As of 1 April 2024, it is available in the B.98 drug program. It may be co-administered with dexamethasone. The response rates and duration are variable; the best results were obtained in younger women [1, 40]. The standard dose is 375 mg/m² four times weekly [40]. Another study has shown splenectomy superior to rituximab, yielding 100% of responses in a small cohort [41]. Practically, if a splenectomy is planned, rituximab should be administered only if the vaccinations were conducted and a timeframe of at least 2 weeks for their action is scheduled. Alternatively, vaccinations can be applied 6 months after completion of the rituximab treatment due to the expected B-cell reconstitution [42].

Mycophenolate mofetil is another immunosuppressive agent inhibiting T-cell proliferation in treating ITP, used less commonly than rituximab. The data on this approach is scarce, and adequate dosing has not been established [43]. The overall response was noted in 56% of the ITP patients in one cohort and 100% (6/6 patients) in a different study (in combination with steroids), with a satisfactory toxicity profile [43, 44].

FOSTAMATINIB

Fostamatinib is a splenic tyrosine kinase (SYK) inhibitor, blocking the cascade of signals mediated by SYK after the activation of FcγRs, reducing macrophage ac-

tivity, the proliferation of B lymphocytes and production of antibodies [45], thereby being effective in second-line treatment of chronic/relapsed ITP. Its use is evaluated among adults; currently, no clinical trials, including children or adolescents, are open/recruiting.

SPLENECTOMY

Currently, splenectomy is treated as a third- or even further-line treatment in autoimmune cytopaenia, including ITP [1]. Because this is a surgical procedure, its benefits and risks should be carefully considered, including the patient's bleeding events and quality of life (present and further), and the reassessment for any other underlying conditions is made, including bone marrow biopsy [1]. Splenectomy is contraindicated in patients younger than 5 years old and/or if the disease lasts less than 12 months [1]. The response to splenectomy is estimated as approximately 80%; however, these data concern splenectomy executed after treatment with steroids. Interestingly, one study reported a higher thrombosis rate after splenectomy in patients previously treated with TPO-RA [46]. Splenectomy also requires specific preparation and a certain platelet level, which can be troublesome in resistance to different medications. Vaccinations against *Neisseria meningitidis* serotypes B and serotypes A, C, W, Y (ACWY), *Haemophilus influenzae*, and *Streptococcus pneumoniae* (PCV-13 or PCV-23, if available) are recommended before splenectomy [1, 47, 48]. Currently, the latter 2 are obligatory in Poland; however, if administered more than 10 years ago, a booster vaccination and supplementing *Neisseria meningitidis* B and ACWY vaccinations are recommended. Antimicrobial prophylaxis after splenectomy is deemed to be controversial, though it is applicable in Poland and worldwide for a year after splenectomy. Usually, oral penicillin is administered to prevent severe bacterial infections; macrolide prophylaxis is adequate for children with an allergy to penicillin [1, 47, 48]. If the response to splenectomy is lost, resulting in a relapse of ITP, the presence of accessory splenic tissue should be considered, and sometimes accessory splenectomy may be a therapeutic option with prior scintigraphy [49].

INHERITED THROMBOCYTOPAENIC DISORDERS MIMICKING IMMUNE THROMBOCYTOPAENIA

A child presenting with isolated, new onset thrombocytopaenia is strongly suggestive of ITP. However, if the treatment fails, inherited thrombocytopaenic disorders need to be reconsidered. We selected and summarised a few of them, which are the most challenging and misleading for clinicians.

The first of them is congenital amegakaryocytic anaemia, an autosomal recessive disease characterised by se-

vere thrombocytopaenia with symptoms such as intracranial bleeding (even *in utero*), epistaxis, and pulmonary haemorrhage [50]. It leads to eventual aplastic anaemia later in life. It is caused by mutations in the *MPL* gene, which codes for the thrombopoietin receptor. Non-haematological symptoms, including mental and psychomotor retardation, are often consequences of intracranial bleeding. The main diagnostic features are increased thrombopoietin levels and a lack of megakaryocytes in the bone marrow [51]. The diagnosis is confirmed by genetic testing. The only curative treatment is an allo-HSCT, which should not be postponed [52]. However, patients with *THPO* mutations may benefit from romiplostim and eltrombopag. Notably, most patients are initially treated with immunoglobulins or steroids, because the presentation may suggest ITP. Certainly, these patients need platelet transfusions and, when the disease progresses, erythrocyte transfusions and antimicrobial prophylaxis due to neutropaenia.

MYH9-related disorders are a group of rare autosomal dominant diseases [53]. The most characteristic features are thrombocytopaenia with large platelets, renal insufficiency, hearing loss, and early-onset cataracts. Due to the fact that *MYH* codes for the non-muscle myosin heavy chain IIa, expressed mainly in podocytes and mesangial cells, chronic kidney disease develops. Such patients are often misdiagnosed with ITP or Alport syndrome [54, 55]. Laboratory findings include large platelets (mean platelet diameter > 3.7 µm), Dohle-like bodies in the neutrophil cytoplasm, MYH9 protein aggregates in the cytoplasm of neutrophils in the immunofluorescence of a peripheral blood smear, and abnormal kidney parameters such as increased creatinine, proteinuria, and microhaematuria are suggestive of this disease [54]. Bleeding can be controlled by various measures. Eltrombopag and oral contraceptives in women can be used to prevent it; however, one should be aware of the increased risk of thrombosis described in *MYH9*-mutated patients. Desmopressin is useful as a prophylaxis for surgeries, but not all patients respond to the treatment. In the case of bleeding, local measures such as compressions and gauze with tranexamic acid are usually enough, but platelet transfusions and antifibrinolytics, for example, tranexamic acid, are recommended as well [54, 55].

Wiskott-Aldrich syndrome (WAS)-related disorders are caused by mutations in the gene encoding the WAS protein (WASp). They affect males due to the X-linked inheritance pattern. There is a vast spectrum of symptoms, and their severity depends on the specific mutation. Classic Wiskott-Aldrich syndrome is the most severe one and is characterised by the triad of immunodeficiency, thrombocytopaenia, and eczema. X-linked thrombocytopaenia and X-linked neutropaenia are milder. When X-linked thrombocytopaenia is concerned, thrombocytopaenia occurs at birth and can present as purpura, petechiae, and epistaxis [56]. Given the lack or small expression of other

symptoms and the usual mild course of the disease, it may be misdiagnosed as ITP. Proper diagnosis is crucial because these patients are still in danger of serious infections, intensive bleeding, malignancies, and autoimmune diseases. Wiskott-Aldrich syndrome disorders need to be considered in male patients with small platelet thrombocytopaenia present at birth or infancy. Haematopoietic stem cell transplantation is the only available curative treatment [57].

Bernard-Soulier syndrome is an autosomal recessive disorder, which is characteristic of large platelets, thrombocytopaenia, and prolonged bleeding time [58]. It is caused by the mutation in genes encoding proteins, which constitute the glycoprotein GPIb-V-IX complex. The incidence is one in a million; however, the disease is often misdiagnosed as ITP or Von Willebrand disease; hence, its real frequency might be underestimated [59]. Main symptoms include epistaxis, prolonged bleeding after dental procedures, menorrhagia, postpartum haemorrhages, and intracranial bleeding after a head trauma. Diagnostics include platelet aggregation study and flow cytometry. Only symptomatic treatment is available, which includes platelet transfusions, and tranexamic acid and hormonal contraception to reduce menorrhagia [60].

CONCLUSIONS

Even though ITP is one of the most common causes of thrombocytopaenia in children, its diagnosis and management may pose a challenge for physicians. The lack of a specific biomarker or test usually makes the diagnosis a diagnosis by exclusion. However, the advent of TPO-RAs and their accessibility has significantly reduced the need for splenectomy, which can be associated with different complications. First- and second-line treatment is now widely available. The most important research directions include an in-depth understanding of the pathogenesis of ITP, finding other treatment options to obtain consistently better results in cITP and rITP, and striving to find a biomarker that can be used for diagnosis.

DISCLOSURES

1. Institutional review board statement: Not applicable.
2. Assistance with the article: None.
3. Financial support and sponsorship: None.
4. Conflicts of interest: None.

REFERENCES

1. Provan D, Arnold DM, Bussel JB, et al. Updated international consensus report on the investigation and management of primary immune thrombocytopenia. *Blood Adv* 2019; 3:3780-3817.
2. Maria L. Lozano. New developments in the diagnosis of primary immune thrombocytopenia. *Blood Coagul Fibrinolysis Int J Haemost Thromb* 2022; 33: S5-7.

3. Grace RF, Lambert MP. An update on pediatric ITP: differentiating primary ITP, IPD, and PID. *Blood* 2022; 140: 542-555.
4. Ibrahim L, Dong SX, O'Hearn K, et al. Pediatric refractory immune thrombocytopenia: a systematic review. *Pediatr Blood Cancer* 2023; 70: e30173.
5. Neunert C, Heitink-Polle KMJ, Lambert MP. A proposal for new definition (s) and management approach to paediatric refractory ITP: reflections from the Intercontinental ITP Study Group. *Br J Haematol* 2023; 203: 17-22.
6. Yang LP, Fu HX, Zhao P, et al. High dimensional single-cell profiling identifies immune and metabolic heterogeneity in immune thrombocytopenia. *Blood* 2023; 142: 2585.
7. Mingot-Castellano ME, Bastida JM, Caballero-Navarro G, et al. Novel therapies to address unmet needs in ITP. *Pharmaceuticals* 2022; 15: 779.
8. Zufferey A, Kapur R, Semple JW. Pathogenesis and therapeutic mechanisms in immune thrombocytopenia (ITP). *J Clin Med* 2017; 6: 16.
9. Imbach P, Crowther M. Thrombopoietin-receptor agonists for primary immune thrombocytopenia. *N Engl J Med* 2011; 365: 734-741.
10. Li Y, Fu J, Ling Y, et al. Sialylation on O-glycans protects platelets from clearance by liver Kupffer cells. *Proc Natl Acad Sci U S A* 2017; 114: 8360-8365.
11. Cooper N, Bussell J. The pathogenesis of immune thrombocytopenic purpura. *Br J Haematol* 2006; 133: 364-374.
12. Castelli R, Lambertenghi Delilliers G, Gidaro A, et al. Complement activation in patients with immune thrombocytopenic purpura according to phases of disease course. *Clin Exp Immunol* 2020; 201: 258-265.
13. Zakaria M, Al-Akhras A, Hassan T, et al. FcγRIIa and FcγRIIIa genes polymorphism in Egyptian children with primary immune thrombocytopenia. *Hematol Transfus Cell Ther* 2023; 45: 58-65.
14. Schmidt DE, Heitink-Pollé KMJ, Laarhoven AG, et al. Transient and chronic childhood immune thrombocytopenia are distinctly affected by Fc-γ receptor polymorphisms. *Blood Adv* 2019; 3: 2003-2012.
15. Li G, Gao L, Ma R, et al. Associations between FCGR polymorphisms and immune thrombocytopenia: a meta-analysis. *Scand J Immunol* 2019; 89: e12758.
16. Hesham M, Hassan T, Fawzy A, et al. PTPN22 gene polymorphism as a genetic risk factor for primary immune thrombocytopenia in Egyptian children. *Expert Rev Hematol* 2021; 14: 877-881.
17. Kim TO, Geris JM, Grimes AB, et al. Genetic variants in canonical wnt signaling pathway associated with pediatric ITP. *Blood* 2023; 142: 2593.
18. Ismail AM, Higazi AM, Nomeir HM, et al. IL-23/Th17 pathway and IL-17A gene polymorphism in Egyptian children with immune thrombocytopenic purpura. *Ital J Pediatr* 2021; 47: 178.
19. Ou Y, Yang Y, Xiang X, et al. Relationship between the IL-10 (-1082 A/G) polymorphism and the risk of immune/idiopathic thrombocytopenic purpura: a meta-analysis. *Cytokine* 2020; 125: 154820.
20. Elnaeay WA, Omar OM, Aboelwafa RA. Increased expression of IL-17A and IL-17F is correlated with RUNX1 and RORγT in pediatric patients with primary immune thrombocytopenia. *J Pediatr Hematol Oncol* 2021; 43: e320-327.
21. Ferreira FLB, Colella MP, Medina SS, et al. Evaluation of the immature platelet fraction contribute to the differential diagnosis of hereditary, immune and other acquired thrombocytopenias. *Sci Rep* 2017; 7: 3355.
22. Hillier K, MacMath D, Chumsky J, et al. Immunoglobulins as a predictor of chronicity in pediatric immune thrombocytopenia. *Blood* 2023; 142: 2370.
23. Kim TO, Grimes AB, Kirk S, et al. Association of a positive direct antiglobulin test with chronic immune thrombocytopenia and use of second line therapies in children: a multi-institutional review. *Am J Hematol* 2019; 94: 461-466.
24. Jones NL, Koletzko S, Goodman K, et al. Joint ESPGHAN/NASPGHAN Guidelines for the Management of Helicobacter pylori in Children and Adolescents (Update 2016). *J Pediatr Gastroenterol Nutr* 2017; 64: 991-1003.
25. González-López TJ, Provan D, Báñez A, et al. Primary and secondary immune thrombocytopenia (ITP): time for a rethink. *Blood Rev* 2023; 61: 101112.
26. Cines DB, Liebman H, Stasi R. Pathobiology of secondary immune thrombocytopenia. *Semin Hematol* 2009; 46: S2-14.
27. Neunert C, Terrell DR, Arnold DM, et al. American Society of Hematology 2019 guidelines for immune thrombocytopenia. *Blood Adv* 2019; 3: 3829-3866.
28. Li T, Liu Q, Pu T, et al. Efficacy and safety of thrombopoietin receptor agonists in children and adults with persistent and chronic immune thrombocytopenia: a meta-analysis. *Expert Opin Pharmacother* 2023; 24: 763-774.
29. Wang Z, Wang N, Ouyang J, et al. Long-term eltrombopag in children with chronic immune thrombocytopenia: a single-center extended real-life observational study in China. *Blood* 2023; 142: 2590.
30. Pines M, Degliuomini M, Kaicker S. Real world practices of thrombopoietin receptor agonist use and discontinuation in pediatric patients with immune thrombocytopenia (ITP): a single center retrospective review. *Blood* 2023; 142: 3960.
31. Neunert CE, Rose MJ. Romiplostim for the management of pediatric immune thrombocytopenia: drug development and current practice. *Blood Adv* 2019; 3: 1907-1915.
32. Nieto M, Calvo G, Hudson I, et al. The European Medicines Agency review of eltrombopag (Revolade) for the treatment of adult chronic immune (idiopathic) thrombocytopenic purpura: summary of the scientific assessment of the Committee for Medicinal Products for Human Use. *Haematologica* 2011; 96: e33-40.
33. Qiu KY, Liao XY, Huang K, et al. Eltrombopag as first-line treatment for thrombocytopenia among paediatric patients after allogeneic haematopoietic stem cell transplantation. *Br J Clin Pharmacol* 2021; 87: 2023-2031.
34. An Q, Liu L, Wang D. PB2623: avatrombopag for the treatment of children with persistent and chronic immune thrombocytopenia. *HemaSphere* 2023; 7: e96683e8.
35. Cheng X, Wang Z, Dong S, et al. Outcomes of switching to avatrombopag following treatment failure with eltrombopag in paediatric immune thrombocytopenia: a real-world study in China. *Br J Haematol* 2023; 202: 636-644.
36. Mingot Castellano ME, Pedrote Amador B, Tomasello R, et al. Avatrombopag plus fostamatinib combination efficacy and safety in patients with immune thrombocytopenia. *Blood* 2023; 142: 2596.
37. Ruan Y, Cao W, Luo T, et al. Avatrombopag for the treatment of thrombocytopenia in children's patients following allogeneic hematopoietic stem-cell transplantation: a pilot study. *Front Pediatr* 2023; 11: 1099372.
38. Jiangsu HengRui Medicine Co., Ltd. Safety and efficacy of hetrombopag in children and adolescents with chronic primary immune thrombocytopenia: a randomized, multicenter, placebo-controlled trial. *clinicaltrials.gov*; 2022.
39. Lei Z. A multicenter, randomized, open-label study to compare the efficacy and safety of TPO-RAs combining anti-CD 20 monoclonal antibody versus TPO-RAs in persistent or chronic pediatric ITP patients who failed or relapse after hormone therapy. *clinicaltrials.gov*; 2023.

40. Lucchini E, Zaja F, Bussel J. Rituximab in the treatment of immune thrombocytopenia: what is the role of this agent in 2019? *Haematologica* 2019; 104: 1124-1135.
41. Ay Y, Karapinar TH, Oymak Y, et al. Retrospective analysis of rituximab therapy and splenectomy in childhood chronic and refractory immune thrombocytopenic purpura. *Blood Coagul Fibrinolysis Int J Haemost Thromb* 2016; 27: 431-435.
42. Nazi I, Kelton JG, Larché M, et al. The effect of rituximab on vaccine responses in patients with immune thrombocytopenia. *Blood* 2013; 122: 1946-1953.
43. Miano M, Ramenghi U, Russo G, et al. Mycophenolate mofetil for the treatment of children with immune thrombocytopenia and Evans syndrome. A retrospective data review from the Italian association of paediatric haematology/oncology. *Br J Haematol* 2016; 175: 490-495.
44. Panigrahi A, Clark A, Myers J, et al. A novel immunomodulatory treatment involving mycophenolate mofetil and corticosteroids for pediatric autoimmune cytopenias. *Pediatr Blood Cancer* 2017; 64: 287-293.
45. pKuwana M, Ito T, Kowata S, et al. Long-term treatment with fostatinib in Japanese patients with primary immune thrombocytopenia: an open-label extension study following a phase 3 placebo-controlled, double-blind, parallel-group study. *Blood* 2023; 142: 2578.
46. Pinedo-Rodríguez A, Pérez-Rojas AK, Rodríguez-Rodríguez S, et al. Determinants of relapse and treatment-free survival following splenectomy in patients with immune cytopenias. *Blood* 2023; 142: 2587.
47. Matkowska-Kocjan A. Profilaktyka zakażeń u dzieci z asplenią 2020. Available from: <http://www.mp.pl/social/article/241654> (accessed: 13.02.2024).
48. Mikołuc B, Bernatowska E, Jackowska T. Profilaktyka zakażeń u pacjentów z asplenią wrodzoną, po splenektomii lub z dysfunkcją śledziony – aktualizacja standardów postępowania. *Stand Med* 2011; 8: 227-233.
49. Choi Y, Dominguez EP, Sherman V, et al. Laparoscopic accessory splenectomy for recurrent idiopathic thrombocytopenic purpura. *JSL* 2008; 12: 314-317.
50. Germeshausen M, Ballmaier M. CAMT-MPL: congenital amegakaryocytic thrombocytopenia caused by MPL mutations – heterogeneity of a monogenic disorder – a comprehensive analysis of 56 patients. *Haematologica* 2021; 106: 2439-2448.
51. Tirthani E, Said MS, De Jesus O. Amegakaryocytic thrombocytopenia. StatPearls, Treasure Island (FL): StatPearls Publishing 2024.
52. Bastida JM, Gonzalez-Porras JR, Rivera J, et al. Role of thrombopoietin receptor agonists in inherited Thrombocytopenia. *Int J Mol Sci* 2021; 22: 4330.
53. Althaus K, Greinacher A. MYH-9 related platelet disorders: strategies for management and diagnosis. *Transfus Med Hemotherapy* 2010; 37: 260-267.
54. Seri M, Pecci A, Di Bari F, et al. MYH9-related disease: May-Hegglin anomaly, Sebastian syndrome, Fechtner syndrome, and Epstein syndrome are not distinct entities but represent a variable expression of a single illness. *Medicine (Baltimore)* 2003; 82: 203-215.
55. Chojnowski K, Klukowska A, Łętowska M, et al. Management of inherited thrombocytopenia. Recommendations of the Group on Hemostasis of the Polish Society of Hematology and Transfusion Medicine, 2019. *J Transfus Med* 2020; 13: 16-28.
56. Malik MA, Masab M. Wiskott-Aldrich Syndrome. StatPearls, Treasure Island (FL): StatPearls Publishing 2024.
57. Bildik HN, Cagdas D, Ozturk Kura A, et al. Clinical, laboratory features and clinical courses of patients with Wiskott Aldrich syndrome and X-linked thrombocytopenia – a single center study. *Immunol Invest* 2022; 51: 1272-1283.
58. Almomani MH, Mangla A. Bernard-Soulier Syndrome. StatPearls, Treasure Island (FL): StatPearls Publishing 2024.
59. Reisi N. Bernard-Soulier syndrome or idiopathic thrombocytopenic purpura: a case series. *Casp J Intern Med* 2020; 11: 105-109.
60. Saridoğan E, Onat T, Arda Düz S, et al. Bernard-Soulier syndrome from the perspective of the obstetrician: a case report with a review of the literature. *Z Geburtshilfe Neonatol* 2023; 227: 168-178.