



Updated Overview about Management of Pediatric Immune Thrombocytopenia

Mervat Atfy Mohammed¹, Shaimaa Saad Abdelhamid¹, Nahla Ibrahim Zidan², Noor Eldin Ahmed Abd El Karim ^{*1}

3171

- 1- Pediatrics Department, Faculty of Medicine - Zagazig University
- 2- Clinical Pathology Department, Faculty of Medicine - Zagazig University

Corresponding Author: Noor Eldin Ahmed Abd El Karim

Email: Mervataty@yahoo.com, noorjad99.nj@gmail.com,

Abstract

Introduction Immune thrombocytopenia (ITP) is an autoimmune hemorrhagic disease due to immune-mediated platelet excessive destruction and inadequate production. The pathogenesis of ITP is relatively complicated, the definite pathogenesis and cause remain unclear up to present. More recent evidences suggest that multiple mechanisms contribute to thrombocytopenia in ITP patients. **Aim:** to assess the prognosis and management of Immune thrombocytopenia among pediatric population. Many studies have found that T-cell subsets, regulatory B cells (Bregs), dendritic cells, myeloid-derived suppressor cells (MDSCs), and natural killer (NK) cells are all involved in the pathogenesis of ITP. First, it has to be determined that there are no blood abnormalities other than a low platelet count, and no physical signs other than bleeding. Then, secondary causes (5–10 percent of suspected ITP cases) should be excluded. Such secondary causes include leukemia, medications (e.g., quinine, heparin), lupus erythematosus, cirrhosis, HIV, hepatitis C, congenital causes, antiphospholipid syndrome, von Willebrand factor deficiency, onyala and others. All patients with presumed ITP should be tested for HIV and hepatitis C virus, as platelet counts may be corrected by treating the underlying disease. In approximately 2.7 to 5 percent of cases, autoimmune hemolytic anemia and ITP coexist, a condition referred to as Evans syndrome. About two out of three pediatric patients with ITP show a spontaneous improvement in platelet count in 6 months without necessity of medical treatment, and those remissions are usually sustained. Most of patients with newly diagnosed ITP do not show signs of bleeding, and can be managed with a “watch and see” strategy. All guidelines support the use of corticosteroids in the first-line treatment of ITP. Immunoglobulins have been used for ITP since 1981, for the effect of modulation on immune system. The treatment induces a raise in platelet count in 80% of pediatric patients, obtaining an effect in the first 48 h more frequent than corticosteroids. Rh-positive children could receive short infusions of anti-D immunoglobulin, with a recommended dose of 50–75 µg/kg. This therapeutic strategy has a response rate greater than 50% and acts more rapidly than IVIG

Keywords: Immune Thrombocytopenia, Pediatric

DOI Number: 10.14704/nq.2022.20.8.NQ44347

NeuroQuantology 2022; 20(8): 3171:3182



Introduction

Immune thrombocytopenia (ITP) is an acquired thrombocytopenia which is defined by the platelet count (PLT) is less than $100 \times 10^9/L$. Primary ITP is an acquired autoimmune disorder characterized by isolated thrombocytopenia caused by increased platelet destruction and impaired platelet production. There is no definitive diagnostic test for ITP; therefore, primary ITP remains a diagnosis of exclusion after ruling out any underlying and/or initiating causes of the thrombocytopenia **(1)**.

In American children, the annual incidence is estimated to be between 1 and 6.4 cases per 100,000 people. Researchers believe pediatric annual incidence is probably higher due to reported cases are based on symptomatic ITP needing hospitalization and not total ITP cases. However, children can present at any age but there is a peak incidence between the ages of 2 years and 5 years as well as another peak in adolescence. In infancy to childhood, there is a slight predominance in males than females **(2)**.

Immune thrombocytopenia (ITP) is an autoimmune hemorrhagic disease due to immune-mediated platelet excessive destruction and inadequate production. the pathogenesis of ITP is relatively complicated, the definite pathogenesis and cause remain unclear up to present. More recent evidence suggest that multiple mechanisms contribute to thrombocytopenia in ITP patients. Increasing studies have found that T-cell subsets, regulatory B cells (Bregs), dendritic cells, myeloid-derived suppressor cells (MDSCs), and natural killer (NK) cells are all involved in the pathogenesis of ITP. **(3)**

Etiology

Etiologic classification divides two categories of ITP: primary ITP and secondary ITP **(4)**.

- The primary form of ITP, classically defined “idiopathic,” is often seen in childhood and triggered by non-specific

viral infections (upper respiratory or gastrointestinal infections): in some cases, acute infections by Epstein–Barr virus, cytomegalovirus, parvovirus, rubella, mumps, and varicella have been identified as triggers of ITP

- Secondary ITP has a complex etiology, as specific infections, drugs or vaccinations and immunologic abnormalities, including immunodeficiencies, can be involved in its pathogenesis.

3172

Bone marrow compensates the platelet destruction by increasing platelet production. ITP most often occurs in healthy children and young adults within a few weeks following a viral infection. ITP is usually manageable with immunosuppressive therapy **(2)**.

A. Infections

Infectious diseases caused by HIV, HCV, *Helicobacter pylori*, and dengue virus can be responsible of secondary ITP, usually with chronic course, through different mechanisms, like molecular mimicry, modulation of the immune system’s activity or suppression of bone marrow production. **(5)**.

B. Drugs

Secondary ITP can be caused by the assumption of drugs and vaccines: drug-induced ITP, as it was referred in most of cases to the assumption of certain antibiotics, non-steroidal anti-inflammatory drugs, and antivirals, it is often not recognized, resulting in recurrent non-explained episodes of thrombocytopenia, that usually show a complete recovery after the withdrawal of the drug. Less commonly than in adulthood, it is possible to observe in childhood the development of heparin-induced thrombocytopenia **(6)**.

Patients who received multiple transfusions are at risk for the development of post transfusion purpura (PTP), a rare form of secondary ITP with a high rate of bleeding: this is more frequent in



multiparous female, but rare reports of PTP with pediatric onset are described (6).

C. Immunodeficiency

Immune thrombocytopenia is a possible manifestation of immunodeficiency, particularly common variable immunodeficiency (CVID), selective IgA deficiency, and DiGeorge's syndrome. It is interesting to underline that, in humoral immune defects; the reduction of platelet count may appear years before the hypo-gammaglobulinemia (7).

D. Autoimmune Diseases

Systemic autoimmune diseases, such as systemic lupus erythematosus (SLE), Sjogren's syndrome, and antiphospholipid syndrome, are associated with the development of ITP: an isolated thrombocytopenia may represent the initial manifestation of SLE, preceding the diagnosis by several years (8).

There may be an association between ITP and clinical and subclinical thyroid autoimmune diseases (Hashimoto's and Basedow-Graves' diseases), suggesting the presence of an overlap in the pathogenesis of these conditions. Moreover, many lymphoproliferative disorders may cause secondary ITP: in this category, the most frequent disease is autoimmune lymphoproliferative syndrome, mostly found in children aged less than 3 years (4).

E. Neoplasia

Lymphoid malignancies, particularly non-Hodgkin's lymphoma, represent a cause of ITP, which rarely can be a paraneoplastic manifestation of a solid neoplasia, mostly in adults (9).

F. Age-Related Considerations

ITP affects approximately four to eight per 100,000 children under the age of 15 each year in the U.S. In neonatal age, the most frequent

form of IT is the alloimmune, caused by the production of maternal antibodies directed against platelet alloantigens. Childhood ITP has an estimated incidence of 4.0– 5.3 per 100,000, while adult ITP has lower incidence of 1.6 – 2.6 per 100,000. ITP in children affects males and females equally, but in infancy males are affected more frequently than females. Childhood ITP has an acute abrupt onset and is commonly preceded few weeks earlier by a viral illness or immunization, such as mumps, measles and rubella (MMR) vaccine. **Fernington et al,(10)** estimated the risk to be 1 in 24,000 doses of MMR vaccine. In a large multi-center study by the International Childhood ITP Registry (ICIS), data was collected from 2031 children with ITP. There were 136 centers from 38 countries participating in the study. Frequency of ITP reached a peak during spring and a nadir during autumn (11).

Diagnosis of ITP:

The diagnosis of ITP is a process of exclusion. First, it has to be determined that there are no blood abnormalities other than a low platelet count, and no physical signs other than bleeding. Then, secondary causes (5–10 percent of suspected ITP cases) should be excluded. Such secondary causes include leukemia, medications (e.g., quinine, heparin), lupus erythematosus, cirrhosis, HIV, hepatitis C, congenital causes, antiphospholipid syndrome, von Willebrand factor deficiency, onyalai and others. All patients with presumed ITP should be tested for HIV and hepatitis C virus, as platelet counts may be corrected by treating the underlying disease. In approximately 2.7 to 5 percent of cases, autoimmune hemolytic anemia and ITP coexist, a condition referred to as Evans syndrome.

Bone marrow examination may be performed on patients who do not respond to treatment, or when the diagnosis is in doubt. On examination of the marrow, an increase in the production of megakaryocytes may be observed and may help in establishing a diagnosis of ITP. An analysis for



anti-platelet antibodies is a matter of clinician's preference, as there is disagreement on whether the 80 percent specificity of this test is sufficient to be clinically useful **(11)**.

Outcome of the patients:

Outcome of ITP patients was assessed by the response to medical therapy.

The following criterion is used to assess outcome of ITP patients and their response to treatment, according to clinical and laboratory parameters:

- **Complete response (CR):** platelet count $\geq 100 \times 10^9/L$ with absence of bleeding.
- **Partial response (PR):** platelet count $\geq 30 \times 10^9/L$ or increase platelet count 2 folds from base line number without bleeding.
- **No response (NR):** platelet count less than $30 \times 10^9/L$ or the increase platelet count is less than 2 fold from base line number or presence of bleeding.

ITP is a primary illness occurring in an otherwise healthy person. Signs of chronic disease, infection, wasting, or poor nutrition indicate that the patient has another illness. Splenomegaly excludes the diagnosis of ITP.

An initial impression of the severity of ITP is formed by examining the skin and mucous membranes, as follows:**(12)**:

1. Widespread petechiae and ecchymoses, oozing from a venipuncture site, gingival bleeding, and hemorrhagic bullae indicate that the patient is at risk for a serious bleeding complication.
2. If the patient's blood pressure was taken recently, petechiae may be observed under and distal to the area where the cuff was placed and inflated.
3. Petechiae over the ankles in ambulatory patients or on the back in bedridden ones suggest mild thrombocytopenia and a

relatively low risk for a serious bleeding complication.

4. The diagnosis of skin and mucous membranes can be by Suction-type electrocardiograph (ECG) leads may induce petechiae.

Although most cases of acute ITP, particularly in children, are mild and self-limited, intracranial hemorrhage may occur in 0.5-1% of children, and half of these cases are fatal.

Findings suggestive of intracranial hemorrhage include the following **(13)**:

1. Headache, blurred vision, somnolence, or loss of consciousness
2. Hypertension and bradycardia, which may be signs of increased intracranial pressure
3. Easy or excessive bruising
4. Superficial bleeding into the skin that appears as pinpoint-sized reddish-purple spots (petechiae) that look like a rash, usually on the lower legs **(Fig.2)**
5. The diagnosis of intracranial hemorrhage can be by neurologic examination, any asymmetrical finding of recent onset or by fundoscopic examination, blurring of the optic disc margins or retinal hemorrhage

ITP was previously known as idiopathic thrombocytopenic purpura or immune thrombocytopenic purpura. ITP without a secondary cause or underlying disorder is known as primary ITP is further categorized into three phases based on the timing and continuation of symptoms. Secondary ITP is defined as ITP with an underlying cause or disorder, which includes drug-induced or systemic illness-induced (eg. SLE, HIV, CVID, etc) **(2)**.

Interview should focus on the potential triggers of ITP (assumption of drugs, vaccines, and transfusions) and risk factors for secondary



forms, as the presence of weight loss, chronic infections (HIV and HCV) and other immune-mediated disease. It is also important to investigate elements suggestive of inherited thrombocytopenia, as previous bleedings and positive familiar history (14).

During physical assessment, the clinician must search potential sites of bleeding (cutaneous and mucosal) and identify signs suggestive for secondary IT or other pathologies, by examining the presence of hepatosplenomegaly, abdominal masses, lymphadenopathies, and bone pain. Furthermore, we analyze the diagnostic the most relevant laboratory investigations in ITP, to introduce our diagnostic algorithm.

A. Laboratory Investigations

1. Full Blood Count

ITP is characterized by isolated thrombocytopenia with normal red blood cells (RBCs) and white blood cells (WBCs) except anemia due to bleeding or iron deficiency (14).

Mean Platelet Volume (MPV)

Mean platelet volume is useful in the first laboratory assessment in patients with ITP and it is usually normal or slightly high (15).

Mean platelet volume (MPV) is one of automated platelet indices that has been investigated by many studies around the achievement of this objective due to its widespread availability.

Analysis of mean platelet volume (MPV) may be helpful in the discrimination between underproduction or over-destruction of platelets as the causes of thrombocytopenia. The primary objective is to find the cut-off point of MPV for distinguishing causes of thrombocytopenia. The secondary objective is to validate the cut-off value of the MPV by using bone marrow (BM) examination. Patients with

BM hypoplasia or thrombocytopenia resulting from cytotoxic drugs or chemotherapy had a low MPV. In contrast, disorders involving the peripheral destruction of platelets had a higher MPV compared to BM diseases (16)

2. Peripheral Blood Smear

Examination of peripheral blood film stained with Wright s or May-Grunwald-Giemsa is the most informative test for distinguishing between ITP and other acquired or inherited thrombocytopenia, the predominant finding is thrombocytopenia with large platelets that is consistent with increase platelet production. Abnormalities in the morphology of red or white blood cells are atypical and should raise suspicion for an alternative diagnosis (17).

Moreover, analysis of blood smear could be useful to assess count and to identify alterations of platelet size and correct measurement of their diameters. Many of congenital thrombocytopenias have also changes in platelet morphology, recognizable with blood smear. The interpretation of blood smear requires experience, and access may be limited in resource poor regions, making it not always applicable as a first-line tool (18).

3. Reticulated Platelet Count (RPLT)

Reticulated platelets are immature platelets circulating in the blood, containing a residual RNA. They can be analyzed with flow cytometry and give an indirect determination of thrombopoietic rate. (Dusse & Freitas) conclude that this is a promising tool to distinguish thrombocytopenia caused by bone marrow hypoproduction to that one due to platelet destruction. Moreover, a study by Thomas-Kaskel et al. demonstrated the correlation between reticulated platelet count and response to treatment (19).

RP will be significantly high in patients with ITP ($1.21 \pm 0.94\%$, $p < 0.01$), especially in active phase ($2.03 \pm 0.88\%$, $p < 0.01$). **Rh (D) Typing**

This exam should be performed in those patients' candidate for receiving therapy with anti-D immunoglobulins. Currently, this treatment is no longer licensed in Europe (20), where Rh typing is not yet recommended.

B. Autoantibodies

Antiplatelet antibodies showed absence of specificity for ITP, and therefore the determination is not routinely recommended. Other autoantibodies, particularly antinuclear (ANA) and antithyroid antibodies, may have a diagnostic role in identifying secondary ITP or, respectively, patients at risk of developing chronic thrombocytopenia and thyroid diseases. Testing for these antibodies is particularly useful in patients with persistent or chronic ITP(21).

C. Bone Marrow Examination

Marrow examination is recommended for those patients who have atypical laboratory or clinical findings such as anemia, neutropenia, splenomegaly. In natural history study of ITP, 296 of 409 patients underwent marrow examination, and this procedure did not result in change in diagnosis. Bone marrow aspiration (BMA) is not required to establish the diagnosis of ITP and also is not necessary prior to steroid treatment in typical cases of ITP. However, BMA should be done if there is bone pain, lymphadenopathy, hepatosplenomegaly, anaemia that is not explained by blood loss, or abnormally high or low WBC (22).

The analysis of bone marrow of a patient with ITP would show an increase in number of megakaryocytes and absence of alterations in other cellular lines. In patients with isolated thrombocytopenia, diagnosis of acute leukemia or lymphoma is unlikely, and bone marrow biopsy and aspirate are rarely useful.

Several authors agree affirming that bone marrow biopsy and aspirate must be performed in children and adolescents with atypical findings for ITP. Moreover, bone marrow examination

should be performed in patients with absence of response to standard treatments, before the beginning of second-line therapies and the execution of splenectomy

D. Bleeding score

The ITP International Working Group (IWG) recommended the use of ITP-specific bleeding assessment tool (ITP-BAT) in evaluating the risk of bleeding

The bleeding symptoms are grouped into 3 major domains: skin (S), visible mucosae (M), and organ (and internal mucosae) (O). In accordance with the WHO bleeding scoring criteria, the severity of bleeding was graded by the SMO scoring system: severe bleeding (affecting vital signs): O (>3); massive bleeding: M (>3); moderate bleeding: S = 3, M = 2, O = 2; mild bleeding: S < 3, M = 1, O = 1; and no bleeding: S = 0, M = 0, O = 0. Rodeghiero et al defined S > 3, M > 1, and O > 1 as hemorrhages of clinical significance (23)

Differential Diagnosis :

Primary ITP in children is a diagnosis of exclusion. The diagnosis of ITP is generally considered in well-appearing child with spontaneous abrupt onset of mucocutaneous bleeding and an isolated, often profound thrombocytopenia. For children with laboratory abnormalities other than thrombocytopenia or with atypical clinical findings, other conditions that can cause thrombocytopenia must be ruled out (23).

The differential diagnosis of thrombocytopenia in pediatric population is very broad. It includes pseudothrombocytopenia (EDTA-induced platelet agglutination), active infection (e.g. infectious mononucleosis, hepatitis, HIV-1), autoimmune hemolytic anemia (Evans syndrome), systemic autoimmune diseases (e.g. systemic lupus erythematosus, antiphospholipid



syndrome), drug exposure (e.g. heparin, quinidine, phenytoin, sulfonamides, vancomycin), bone marrow failure syndromes (e.g. aplastic anemia, myelodysplastic syndrome), consumptive processes (e.g. hemolytic uremic syndrome, thrombotic thrombocytopenic purpura, disseminated intravascular coagulation), immunodeficiency syndromes (e.g. common variable immunodeficiency, Wiscott Aldrich syndrome), and inherited thrombocytopenic disorders (e.g. inherited aplastic anemia, thrombocytopenia-absent radius syndrome, von Willebrand disease type 2B) **(23)**.

The clinical step remains fundamental: in case of severe bleeding signs, it is mandatory to treat the patient, and the required investigations are different (see Consideration on Patients with Acute Bleeding). Moreover, if anamnesis or physical assessment shows elements indicative for secondary IT (abdominal masses and adenopathies), the algorithm becomes not necessary, and the laboratory and radiological approach must start with investigations directed to confirm the etiologic hypothesis suggested by the clinical findings **(24)**.

The second step comprehends laboratory exams directed to identify the conditions that more frequently cause secondary IT and non-ITP, including inherited thrombocytopenia, infections, immunodeficiency, and lymphoid malignancies.

The third step includes an abdominal echography, useful to recognize alterations in liver, spleen, and abdominal lymph nodes, not always appreciable during clinical examination. This step also considers the determination of reticulated platelet count: despite the lack of standardization of values and difficulties in interpretations, this investigation, when available, can give important information about thrombopoietic rate, and thus remains an option to consider **(24)**.

The last step comprehends investigations for autoimmune diseases and chronic infections. Determination of ANA is also important to predict the evolution to a chronic form **(24)**.

I. Complications

The majority of complications associated with ITP in both children and adults is correlated to the bleeding risk associated with low platelet counts, specifically when the platelet count is less than 20,000/microL. **(2)**.

In some severe cases, patients may have gastrointestinal tract bleeding causing hemepositive stools, hematuria, or menorrhagia. The most feared complication of ITP is intracranial hemorrhage (ICH). In newly diagnosed children, the risk of ICH is about 0.5% and is slightly increased in those children with chronic ITP, but still less than 1%. Most cases of ICH occur at platelet levels less than 10,000/microL.

Symptoms concerning for ICH in both children and adults include headache, persistent vomiting, altered mental status, seizures, focal neurological findings, and/or recent head trauma **(2)**.

Treatment

About two out of three pediatric patients with ITP show a spontaneous improvement in platelet count in 6 months without necessity of medical treatment, and those remissions are usually sustained. Most of patients with newly diagnosed ITP do not show signs of bleeding, and can be managed with a “watch and see” strategy.

There is no absolute consensus about the platelet threshold necessary to start treatment in ITP: 1996 guidelines of the American Society of Hematology recommended treating patients with a platelet count lower than 10,000/ μ l and minor purpura or those one with a count lower 20,000/ μ l and significant bleeding **(25)**.

Children with ITP should be restricted from activities associated with a bleeding risk from trauma when their platelet count is less than 30,000/microL. These activities include but are not limited to contact and collision sports (i.e. football, boxing, lacrosse, and hockey) or any other activities associated with a risk for head injury (i.e. baseball, soccer, skiing or gymnastics). Both children and adults should avoid antiplatelet medications, which include aspirin, ibuprofen, and other nonsteroidal anti-inflammatories (NSAIDs). Anticoagulants (i.e. heparin, enoxaparin, warfarin) should also be avoided in patients with platelet counts less than 20,000/microL (2).

A. First-line treatment

1. Prednisone–Prednisolone

All guidelines support the use of corticosteroids in the first-line treatment of ITP. Oral prednisone is often effective in inducing response in pediatric patients when administered at doses of 1–2 mg/kg for 7–14 days and maintains efficacy also at higher doses (4 mg/kg/day) for 3 or 4 days, raising platelet count over 50,000/ μ l in the first 72 h in 72–88% of patients. However, due to the adverse effects of a prolonged treatment with corticosteroids in children, those drugs must be used only for short periods, to maintain a hemostatic platelet count (26).

Corticosteroids

Corticosteroids act by reducing antibody production and preventing platelet destruction by macrophages. Available corticosteroids include prednisone, prednisolone. (26).

Dosage:

Oral prednisone or intravenous methylprednisolone, split into 3 doses given after breakfast, lunch and dinner. Dose of 4 mg/kg/day (to a maximum of 180 mg/day) given for 4 days, followed by 2 mg/kg for 3 days and discontinuation. Steroid bolus:

methylprednisolone 30 mg/kg/day to maximum of 1 g, for 3 days, infused over 2 h. It requires monitoring of blood pressure and glucose in urine. Oral dexamethasone: 0.6 mg/kg/day to a maximum of 40 mg given in a single dose for 4 days. It is usually given in monthly cycles (26).

Use of long-term corticosteroids should be avoided when possible due to significant adverse effects, such as osteoporosis, diabetes, hypertension, and weight gain. For patients who do not maintain a stable platelet count after initial therapy with corticosteroids, IVIG therapy can be considered until a second-line treatment option may be given. This same principle can be considered in patients unable to tolerate the adverse effects of corticosteroids (26).

2. Intravenous Immunoglobulins (IVIg)

Immunoglobulins have been used for ITP since 1981, for the effect of modulation on immune system. The treatment induces a raise in platelet count in 80% of pediatric patients, obtaining an effect in the first 48 h more frequent than corticosteroids.

IVIg are usually administered in a single dose of 0.8–1 g/kg, with the chance of using a second dose in case of incomplete response, even if also lower doses (0.6 g/kg) are reported to be effective. Adverse effects include headache and fever and are more common when used doses are greater than 1 g/kg for consecutive days (4).

Most common side effects being headaches, chills, arthralgia, and back pain. Serious complications, specifically thrombotic events, are rarely observed (26).

3. Intravenous Anti-D Immunoglobulin



Rh-positive children could receive short infusions of anti-D immunoglobulin, with a recommended dose of 50–75 µg/kg. This therapeutic strategy has a response rate greater than 50% and acts more rapidly than IVIG. However, in patients with comorbidity, the treatment has been associated with severe hemolysis, acute renal failure, and disseminated intravascular coagulation, and therefore anti-D immunoglobulin administration should require a careful selection of patients and post-therapy monitoring, as concluded by **Despotovic et al (25)**.

Adverse effects:

Immune haemolytic anaemia and, since this is a blood derivative, there is a risk of transmission of infectious diseases. There are also reported cases of hepatitis C transmission. **(26)**

B. Second-line Therapies

1. Rituximab

This anti-CD20 antibody, used in other autoimmune diseases and B-cell lymphoma, has been used in chronic refractory ITP often showing response rates greater than 60%, even though in a study by Bennett et al. only 31% of patients responded. However, follow-up studies have shown that sustained response is uncommon, and safety profile is unclear **(27)**.

2. Danazol

This attenuated androgen is successfully used in second-line treatment of adult patients with ITP, particularly in elderly patients. There are only a few studies about its use in pediatric patients, showing a good effectiveness without significant adverse reactions. Unfortunately, danazol can accelerate bone growth, and this limits its applicability in prepuberal patients.

3. Thrombopoietin Receptor Agonists (TPO-RAs)

Since the discovery of the role of thrombopoietin (TPO) in ITP several thrombopoietic drugs was tested, and in 2008 FDA approved two TPO receptor agonists for non-responsive ITP in adults: romiplostim and eltrombopag. Romiplostim acts on TPO-binding subunit of the receptor and is administered subcutaneously weekly **(28)**.

Eltrombopag acts binding the transmembrane domain of TPO receptor and is administered orally daily. It showed response rates greater than 60% in two randomized trials, associated with a good tolerability, so in 2015 FDA has approved it for the use in childhood-onset disease. Reported adverse effects consist in an increased risk of hepatic damage and cataract. Recently, avatrombopag, a new drug with an eltrombopag-like mechanism of action, was included in clinical trials for adults, showing response rate similar to other TPO-RAs in absence of severe adverse effects. In summary, TPO-RAs seem to be safe and effective also in childhood-onset refractory ITP.

4. Use of Immunosuppressors

There are only a few studies investigating the role of immunosuppressive agents, single or in combination, in patients with refractory ITP, and experience in childhood is not enough strong to give specific recommendations **(22)**. Azathioprine, used in several autoimmune pediatric diseases, is still an option for the treatment of adult patients with ITP, particularly in chronic ITP and when splenectomy is contraindicated or has been ineffective. Response is detectable after about 4 months, and adverse effects, such as posttreatment leukemia, are extremely rare **(22)**.

In pediatric age, cyclosporine is used in several conditions (organ transplants, autoimmune hepatitis, acquired aplastic anemia, juvenile dermatomyositis, and nephrotic syndrome) while its applicability in ITP is not completely defined. In adult patients, this drug often shows positive response rates both in single therapy



and in association with steroids, with possibility of sustained remission after discontinuation of treatment. Despite the lack of evidence in childhood-onset ITP and the necessity of further studies, these data support the potential utility of immunosuppressive agents as a second-line treatment in refractory ITP (4).

5. Splenectomy

Several studies reported a response in almost 85% of patients after splenectomy, with a 20–25% of relapses during the following years. Many works investigated the role of potential predictors of response to splenectomy in children and adults and suggested that female sex, younger age, response to steroids, and higher platelet count could be positive prognostic determinants, although the role of response to steroids is not univocally accepted (29).

Patients who received splenectomy are at risk of developing relevant adverse effects, particularly infections and sepsis by capsulated bacteria, with reported mortality rates of 3%, and thus the procedure is rarely recommended in children, being usually performed only in selected cases.

C. New Therapeutic Targets

There are ongoing trials about other classes of drugs for ITP, currently limited to application in adulthood. New potential targets are represented by interaction between T-cells and antigen-presenting cells (anti-CD40L antibodies), platelet phagocytosis [SYK inhibitors and interference with FcR binding on macrophages, activation of B-cells (anti-CD52 or alemtuzumab) and T-cells [anti-IL-2R or daclizumab, and TH1 expansion (anti-CD16) (30).

Multiagent Therapy:

Dexamethasone and Rituximab:

The combination of rituximab and high-dose dexamethasone augments response rates at 6 and 12 months compared with dexamethasone alone or rituximab alone in patients with ITP. Longer follow-up is required to determine whether combination therapy leads to cure in an additional proportion of patients compared with either agent alone or merely postpones relapse (31).

In a single-arm Mexican study, 21 patients were treated with one cycle of high-dose dexamethasone and low-dose rituximab (100mg) weekly 4weeks. A second cycle of high-dose dexamethasone was permitted if the platelet count was $< 20 \times 10^9/L$ before day 30. A complete response (platelet count $100 \times 10^9/L$) at 6 months was attained in 16 (76%) patients. Freedom from relapse (platelet count $< 30 \times 10^9/L$) was 84% at 12 months (32).

Dexamethasone and Thrombopoietin Receptor Agonist:

A combination of dexamethasone and eltrombopag has been tested in a prospective single-arm study. Twelve Mexican with newly diagnosed ITP were treated with a single cycle of dexamethasone 40 mg daily on days 1 to 4 followed by eltrombopag 50 mg daily on days 5 to 32. A sustained response (platelet count $30 \times 10^9/L$) was observed in 9 (75%) patients at 6 months and 8 (67%) patients at 12 months. These preliminary findings require confirmation in a larger controlled study (32).

References



1. Terrell, D. R., Neunert, C. E., Cooper, N., Heitink-Pollé, K. M., Kruse, C., Imbach, P., Kühne, T., & Ghanima, W. (2020). Immune Thrombocytopenia (ITP): Current Limitations in Patient Management. *Medicina (Kaunas, Lithuania)*, 56(12), 667.
2. Pietras, N. M., & Pearson-Shaver, A. L. (2020). Immune Thrombocytopenic Purpura. *StatPearls*, 1.
3. Wan, Z., Song, L., Hu, L., Lei, X., Huang, Y., Lv, Y., & Yu, S. (2021). The role of systemic inflammation in the association between serum 25-hydroxyvitamin D and type 2 diabetes mellitus. *Clinical Nutrition*, 40(6), 3661–3667.
4. Consolini, R., Costagliola, G., & Spatafora, D. (2017). The centenary of immune thrombocytopenia—part 2: revising diagnostic and therapeutic approach. *Frontiers in Pediatrics*, 5, 179.
5. Abdollahi, A., Shoar, S., Ghasemi, S., & Zohreh, O.-Y. (2015). Is *Helicobacter pylori* infection a risk factor for idiopathic thrombocytopenic purpura in children? *Annals of African Medicine*, 14(4), 177.
6. Reese, J. A., Nguyen, L. P., Buchanan, G. R., Curtis, B. R., Terrell, D. R., Vesely, S. K., & George, J. N. (2013). Drug-induced thrombocytopenia in children. *Pediatric Blood & Cancer*, 60(12), 1975–1981.
7. Patuzzo, G., Barbieri, A., Tinazzi, E., Veneri, D., Argentino, G., Moretta, F., Puccetti, A., & Lunardi, C. (2016). Autoimmunity and infection in common variable immunodeficiency (CVID). *Autoimmunity Reviews*, 15(9), 877–882.
8. Fayyaz, A., Igoe, A., Kurien, B. T., Danda, D., James, J. A., Stafford, H. A., & Scofield, R. H. (2015). Haematological manifestations of lupus. *Lupus Science & Medicine*, 2(1), e000078.
9. Nenova, I. S., Valcheva, M. Y., Beleva, E. A., Tumbeva, D. Y., Yaneva, M. P., Rancheva, E. L., & Grudeva-Popova, Z. G. (2016). Autoimmune phenomena in patients with solid tumors. *Folia Medica*, 58(3), 195.
10. Ferreira, F. L. B., Colella, M. P., Medina, S. S., Costa-Lima, C., Fiusa, M. M. L., Costa, L. N. G., Orsi, F. A., Annichino-Bizzacchi, J. M., Fertrin, K. Y., & Gilberti, M. F. P. (2017). Evaluation of the immature platelet fraction contribute to the differential diagnosis of hereditary, immune and other acquired thrombocytopenias. *Scientific Reports*, 7(1), 1–8.
11. Sokal A, de Nadaï T, Comont T, Limal N, Michel M, Beyne-Rauzy O, Godeau B, Adoue D, Mahévas M, Moulis G, investigators Group C. Immune Thrombocytopenia in Very Elderly Patients: Particularities in Presentation and Management. Results from the Multicenter Perspective Carmen-France Registry. *Blood*. 2019 Nov 13; 134:1091.
12. Sugiura, T., Yamamoto, K., Murakami, K., Horita, S., Matsusue, Y., Nakashima, C., & Kirita, T. (2018). Immune Thrombocytopenic Purpura Detected with Oral Hemorrhage: a Case Report. *Journal of Dentistry (Shiraz, Iran)*, 19(2), 159–163.
13. Edlow, J. A., Rabinstein, A., Traub, S. J., & Wijdicks, E. F. M. (2014). Diagnosis of reversible causes of coma. *The Lancet*, 384(9959), 2064–2076.
14. Jawed, M., Khalid, A., Rubin, M., Shafiq, R., & Cemalovic, N. (2021). Acute immune thrombocytopenia (ITP) following COVID-19 vaccination in a patient with previously stable ITP. *Open Forum Infectious Diseases*, 8(7), ofab343.
15. Noris, P., Melazzini, F., & Balduini, C. L. (2016). New roles for mean platelet volume measurement in the clinical practice? *Platelets*, 27(7), 607–612.
16. Norrasethada, L., Khumpoo, W., Rattarittamrong, E., Rattanathammethee, T., Chai-Adisaksopha, C., & Tantiworawit, A. (2019). The use of mean platelet volume for distinguishing the causes of thrombocytopenia in adult patients. *Hematology Reports*, 11(1).
17. Geddis, A. E., & Balduini, C. L. (2007). Diagnosis of immune thrombocytopenic purpura in children. *Current opinion in hematology*, 14(5), 520–525.
18. Zaninetti, C., & Greinacher, A. (2020). Diagnosis of inherited platelet disorders on a blood smear. *Journal of Clinical Medicine*, 9(2), 539.
19. Dusse, L. M. S., & Freitas, L. G. (2015). Clinical applicability of reticulated platelets. *Clinica Chimica Acta*, 439, 143–147.
20. Labarque, V., & Van Geet, C. (2014). Clinical practice: immune thrombocytopenia in paediatrics. *European Journal of Pediatrics*, 173(2), 163–172.
21. Lambert, M. P., & Gernsheimer, T. B. (2017). Clinical updates in adult immune thrombocytopenia. *Blood, The Journal of the American Society of Hematology*, 129(21), 2829–2835.
22. Provan D., Arnold D.M., Bussel J.B., Chong B.H., Cooper N., Gernsheimer T., Ghanima W., Godeau B., González-López T.J., Grainger J. (2019) Updated international consensus report on the investigation and management of primary immune thrombocytopenia. *Blood Adv.*; 3:3780–3817.
23. Huang J, Zeng B, Li X, Huang M, Zhan R. (2020) Comparative Study of the Clinical Application of 2 Bleeding Grading Systems for Pregnant Women with Immune Thrombocytopenia. *Clinical and Applied Thrombosis/Hemostasis*.
24. Neunert, C. E. (2017). Management of newly diagnosed immune thrombocytopenia: can we change outcomes? *Blood Advances*, 1(24), 2295–2301.
25. Despotovic, J. M., & Grimes, A. B. (2018). Pediatric ITP: is it different from adult ITP? *Hematology 2014, the American Society of Hematology Education Program Book*, 2018(1), 405–411.
26. Khan, A. M., Mydra, H., & Nevarez, A. (2017). Clinical practice updates in the management of immune thrombocytopenia. *Pharmacy and Therapeutics*, 42(12), 756.
27. Lucchini, E., Zaja, F., & Bussel, J. (2019). Rituximab in the treatment of immune thrombocytopenia: what is



the role of this agent in 2019? *Haematologica*, 104(6), 1124.

28. **Garzon, A. M., & Mitchell, W. B. (2015).** Use of thrombopoietin receptor agonists in childhood immune thrombocytopenia. *Frontiers in Pediatrics*, 3, 70.
29. **Ahmed, R., Devasia, A. J., Viswabandya, A., Lakshmi, K. M., Abraham, A., Karl, S., Mathai, J., Jacob, P. M., Abraham, D., Srivastava, A., Mathews, V., & George, B. (2016).** Long-term outcome following splenectomy for chronic and persistent immune thrombocytopenia (ITP) in adults and children: Splenectomy in ITP. *Annals of Hematology*, 95(9), 1429–1434.
30. **Newland, A., Lee, E. J., McDonald, V., & Bussel, J. B. (2018).** Fostamatinib for persistent/chronic adult immune thrombocytopenia. *Immunotherapy*, 10(1), 9–25.
31. **Prak, E., Cines, D., & Cuker, A. (2015).** Can Immune Thrombocytopenia Be Cured with Medical Therapy? *Seminars in Thrombosis and Hemostasis*, 41(04), 395–404.
32. **Gómez-Almaguer D, Herrera-Rojas MA, Jaime-Pérez JC, et al. (2014).** Eltrombopag and high-dose dexamethasone as frontline treatment of newly diagnosed immune thrombocytopenia in. *Blood*;123(25):3906–3908.

