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Immune Thrombocytopenia in Children: Pathophysiology, Diagnosis and Contemporary Management; A Narrative Review

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Abstract

Background: Immune thrombocytopenia (ITP) is an acquired disorder characterized by isolated thrombocytopenia, with a platelet count below 100 × 10^9/L. The disease may be primary or associated with other conditions, and its clinical course varies according to age and duration. Platelet loss is not explained by a single mechanism: antiplatelet antibodies, complement activation, altered T-cell responses, and impaired megakaryocyte function may all contribute to thrombocytopenia. In children, accurate recognition of these mechanisms must be considered alongside the exclusion of alternative causes of a low platelet count.

Objective: To review the definition and classification of ITP, the mechanisms underlying immune-mediated platelet destruction and reduced platelet production, and the principal approaches to diagnostic assessment, clinical evaluation, prognosis, and management described in the supplied literature chapters.

Conclusion: ITP represents a heterogeneous immune disorder in which antibody-mediated clearance, cellular immune dysregulation, and defective platelet production interact. Diagnosis remains primarily clinical and requires careful history taking, physical examination, complete blood count, peripheral blood smear review, and selective investigation for secondary causes. Disease duration, bleeding manifestations, and the possibility of alternative diagnoses are important considerations in assessment and follow-up. A clearer understanding of the different pathogenic pathways may support more individualized management, while the variability of clinical course emphasizes the need to interpret laboratory findings in the context of each patient.

Keywords: Immune thrombocytopenia; Pediatric ITP; Platelet destruction; Autoimmunity

Introduction:

Definition and Classification

Immune thrombocytopenic purpura (ITP) is a condition acquired characterized by isolated thrombocytopenia, defined by a peripheral blood platelet count of less than 100 x 109/L, in the absence of any evident initiating or underlying factors. Nevertheless, ITP may occur alongside other predisposing conditions. ITP can be characterized as either primary (idiopathic) or secondary to a number of associated disorders such as immunodeficiency diseases, autoimmune rheumatologic disorders, lymphoproliferative diseases, and certain chronic infections. [(1)]

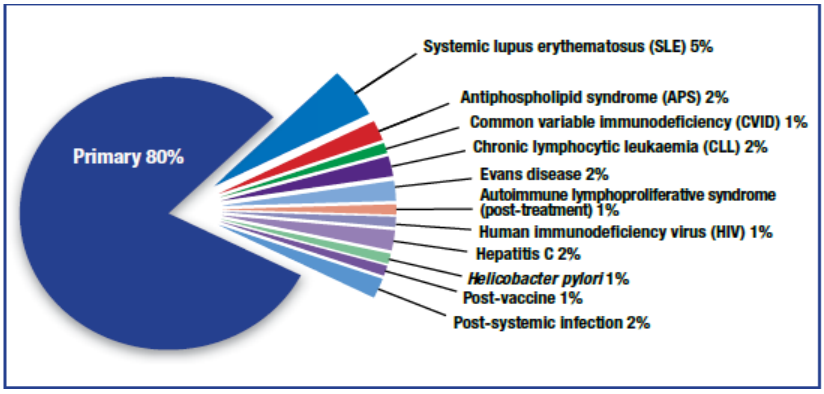


Figure 1. Estimated proportion of different causes of secondary ITP.

III- Classification of ITP:

ITP can be classified into primary and secondary categories, with the classification also considering the duration of the disease. This duration is further divided into three phases: newly diagnosed (0-3 months), persistent (>3-12 months), and chronic (>12 months). The term "refractory" is applied to patients who do not show a sufficient response to splenectomy [(1)].

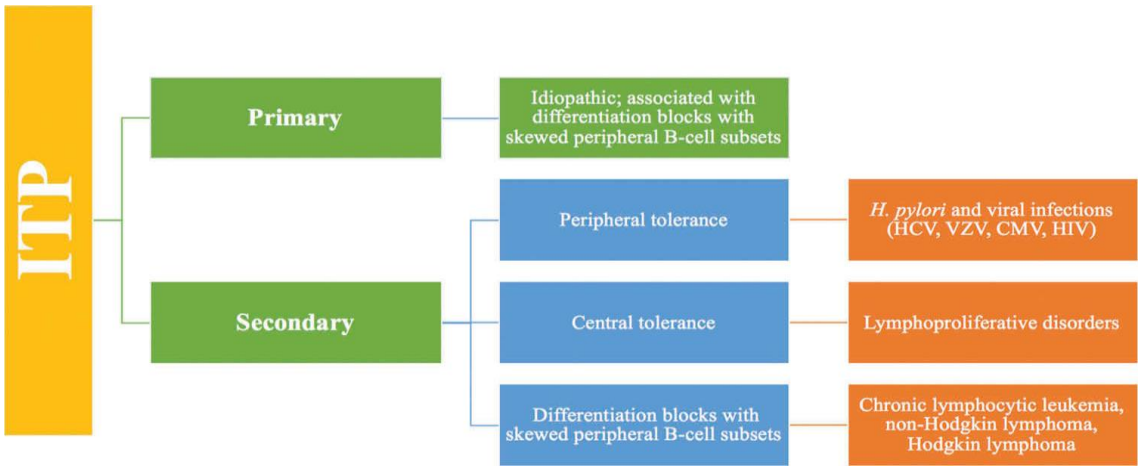


Figure 2. Classification of ITP. ITP is divided into an idiopathic primary form associated with differentiation blocks, and a secondary form involving immune tolerance defects or skewed B-cell subsets. ITP: idiopathic/immune thrombocytopenic purpura; HCV: hepatitis C virus; VZV: varicella-zoster virus; CMV: cytomegalovirus; HIV: human immunodeficiency virus.

The worldwide occurrence of secondary immune thrombocytopenic purpura (ITP) demonstrates significant disparities, especially in demographics with high prevalence rates of HIV, hepatitis C virus (HCV), or Helicobacter pylori infections. There is a scarcity of data concerning the incidence or prevalence of ITP in areas beyond North America and Europe. In adult populations, the prevalence of ITP is markedly elevated compared to that in children, largely due to the chronic nature of the disease among adults. Reports indicate that the annual incidence of newly diagnosed ITP in adults ranges from 1.6 to 3.9 cases per 100,000 individuals.

Pathophysiology of ITP:

- **Peripheral destruction of platelets**

a) Humoral response and antiplatelet antibodies

b) T-cell immune dysregulation

- Inappropriate platelet bone marrow production

Humoral response and antiplatelet antibodies

The participation of the humoral response in relation to platelets has been recognized since the 1950s, when Harrington and colleagues discovered that serum from patients with immune thrombocytopenic purpura (ITP) caused thrombocytopenia when administered to healthy individuals. [(2)].

The study additionally demonstrated that Immunoglobulin G (IgG) plays a critical role in this effect by interacting with several platelet glycoproteins, particularly GPIIb/IIIa (the fibrinogen receptor), GPIb/IX (the von Willebrand factor receptor), and to a lesser extent, GPIa/IIa (the collagen receptor) as well as GPIV [(3)]. In clinical settings, the direct monoclonal antibody immobilization of platelet antigens assay (MAIPA) facilitates the identification of antiplatelet antibodies in approximately 85% of patients with immune thrombocytopenic purpura (ITP). This assay demonstrates positivity for antibodies against GPIIb/IIIa in 66.7% of instances, GPIb/IX in 60%, GPIa/IIa in 40.6%, and GPIV in 26.9% [(3)]. Recent studies have identified the presence of anti-GPV antibodies in patients with immune thrombocytopenic purpura (ITP). In the majority of instances, these antibodies were found to correlate with anti-GPIb/IX antibodies, while only 2.9% of patients exhibited these as the sole type of antiplatelet antibody. Although their affinity for platelets is comparatively lower, their role in platelet destruction has been corroborated through investigations conducted in murine models [(4)].

The spleen is vital in the pathogenesis of immune thrombocytopenic purpura (ITP), serving as the focal point for a robust autoimmune reaction characterized by the proliferation of germinal centers and the production of mutated, high-affinity plasma cells that secrete antiplatelet antibodies. A portion of these plasma cells migrate to the bone marrow, where they may persist as long-lived plasma cells. While instances of IgM antiplatelet antibodies have been noted, the predominant antibody type is IgG, particularly IgG1, which is found in 77% of cases and is associated with somatic hypermutation in their variable immunoglobulin genes. Furthermore, splenic T follicular helper cells (TFHs) are implicated in the selection of autoreactive B-cell clones within the germinal centers [(5)]. Different mechanisms facilitate the antibody-mediated cytotoxicity, including complement-dependent cytotoxicity (CDC), which leads to the elimination of target cells through the assembly of the membrane attack complex (MAC) [(6)], Moreover, it promotes the phagocytosis of these cells through antibody-dependent cellular phagocytosis (ADCP) mediated by macrophages that express Fc gamma receptors (FcγR) and complement receptor 1, which interacts with the complement component C3b. Conversely, the mechanism of antibody-dependent cellular cytotoxicity (ADCC), facilitated by natural killer (NK) cells, is likely to play a lesser role in the context of immune thrombocytopenic purpura (ITP) [(7)].

The role of complement was explored during the 1980s and remains a topic of significant relevance today, particularly as complement inhibitors have advanced into clinical trials. It has been documented that the sera of patients with Immune Thrombocytopenic Purpura (ITP) activate the classical complement pathway in approximately 50% to 60% of cases, as determined by the deposition of complement components on platelets. This activation shows a correlation with the presence and specific type of antiplatelet antibodies; it is observed in 33% of cases when such antibodies are absent and rises to 81% when they are present in the sera. Notably, antibodies targeting GPIIb/IIIa are more effective at activating complement pathways compared to those targeting GPIb/IX, with activation rates of 73% to 100% for the former and 40% to 65% for the latter (8). A principal pathway for the destruction of peripheral platelets is antibody-dependent cellular phagocytosis (ADCP), which is facilitated by splenic macrophages. Recent findings in human studies affirm that phagocytosis occurs through the binding of opsonized platelets to FcγRI and FcγRIII receptors, while no involvement of FcγRII is observed.25 In addition to their phagocytic capabilities, splenic macrophages significantly contribute to their function as primary antigen-presenting cells (APCs) in the context of immune thrombocytopenic purpura (ITP) (9). Ex vivo isolation of splenic macrophages from patients with immune thrombocytopenic purpura (ITP) demonstrates a significantly enhanced capacity to promote the proliferation of anti-GPIIb/IIIa T-cell clones when contrasted with dendritic cells and B cells, which necessitate prior loading with antigens.

T-cell immune dysregulation

The involvement of CD4 T cells in Immune Thrombocytopenic Purpura (ITP) has been documented for several years, with studies from the early 2000s identifying clones that target GPIIb/IIIa in the spleen and blood of individuals diagnosed with ITP. Notably, among patients who respond positively to splenectomy, there is a marked reduction in the frequency of these circulating clones, underscoring their role in the autoimmune mechanism and suggesting that they may also inhabit locations beyond the spleen (10). As is common in various autoimmune disorders, ITP is characterized by an imbalance between proinflammatory and anti-inflammatory responses. In this context, there is a noted shift in T cells towards helper T cell (Th) 1 and Th17 subtypes, which coincides with a quantitative or functional deficit of regulatory T cells (Treg). This deficiency of Tregs contributes to the persistence of the autoimmune process across multiple sites, including the blood, spleen, and bone marrow in patients with ITP. Intriguingly, the deficiency of Tregs demonstrates improvement when treated with dexamethasone, rituximab, or thrombopoietin receptor agonists (TPO-RA). Additionally, the therapeutic response to rituximab is linked to a reversal of Th1 polarization.

TFH cells proliferate within the germinal centers of the spleen, where they promote the differentiation of B cells into plasma cells that produce antiplatelet antibodies. This process necessitates the interaction between CD40, which is present on B cells, and CD154, found on TFH cells, in conjunction with the secretion of IL-21 by TFH [(11)]. Furthermore, it has been noted that the presence of TFH cells in the spleen is contingent upon the presence of B cells, as evidenced by the absence of TFH in the spleens of ITP patients undergoing rituximab treatment [(12)]. Consequently, it remains plausible that following rituximab therapy, memory TFH cells with altered phenotypes persist within the spleen, potentially regaining their standard phenotypic characteristics and functions upon B cell reconstitution. This phenomenon may contribute to the relapse of ITP observed in certain patients after an initial favorable response to rituximab.

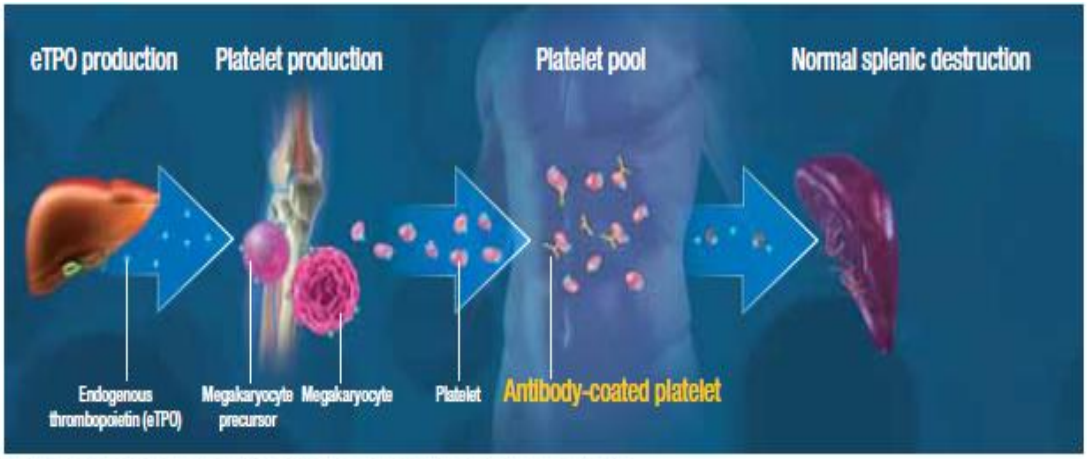
The involvement of cytotoxic T lymphocytes (CTL) in ITP was established in the early 2000s, evidenced by their ability to lyse platelets, coupled with elevated plasma levels of cytotoxic proteins granzyme A and B [(13)]. However, a critical concern is the ability of CTL to target an adequate number of platelets to initiate thrombocytopenia, given that effective CTL cytotoxicity necessitates close cellular proximity, with a CTL: platelet ratio of 1:100 to 1:400 observed in circulation. It is therefore conceivable that CTL-mediated cytotoxic effects may occur within the spleen, where the tissue architecture may facilitate closer interactions between cells. Notably, a rise in IFN-γ-secreting CD8 T cells, characterized as cytotoxic T cells with a memory phenotype and granzyme B expression, was observed in patients resistant to rituximab, thereby indicating a T cell-mediated pathology as opposed to a B cell-driven process in these individuals[(14)].

In addition to the peripheral destruction of platelets, CTL cytotoxicity also adversely impacts megakaryocytes. This relationship is supported by the increased recruitment of megakaryocytes to the bone marrow, which is mediated by fractalkine, a chemokine that binds to CX3CR1 expressed on CTL, thereby influencing platelet production.

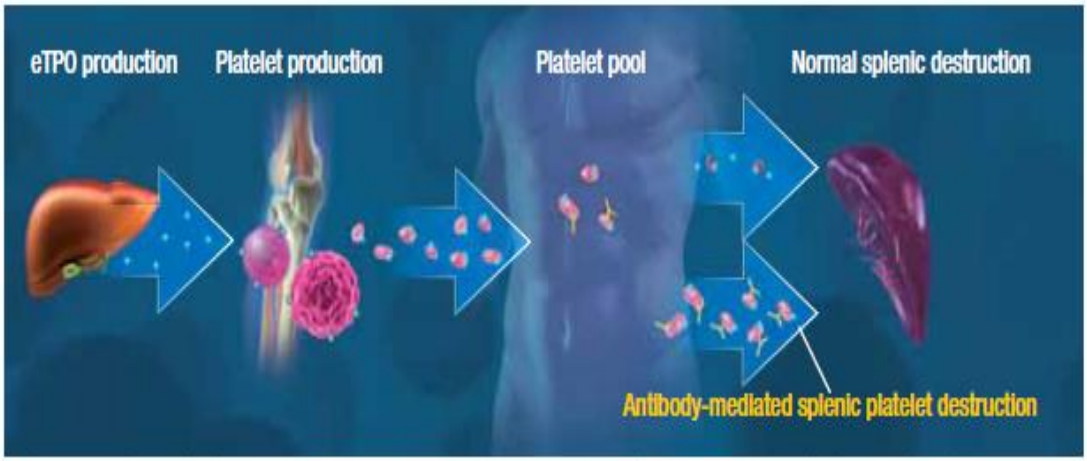
Inappropriate platelet bone marrow production:

In conjunction with the peripheral destruction of platelets, Immune Thrombocytopenic Purpura (ITP) is characterized by inappropriate platelet production, which stems from an immune response targeting megakaryocytes as well as insufficient levels of thrombopoietin (TPO). During ITP, the abnormal levels of TPO can be attributed to its physiological regulation mechanisms. The production of TPO by hepatocytes is prompted by the identification of aging, desialylated platelets by the Ashwell-Morell receptor (AMR). TPO exerts its effects on megakaryocytes by binding to the cMpl receptor, which is also present on platelets. Consequently, the circulating platelet pool is instrumental in its own regulation: in instances of thrombocytopenia, elevated levels of unbound TPO are available to megakaryocytes, thereby enhancing platelet production. Conversely, in cases of thrombocytosis, a significant amount of TPO binds to platelets, resulting in a limited quantity of free TPO available to stimulate megakaryocytes. Pertinently, in ITP, the volume of platelets in circulation is comparable to normal levels, which facilitates high levels of TPO binding to rapidly destroyed platelets, ultimately leading to

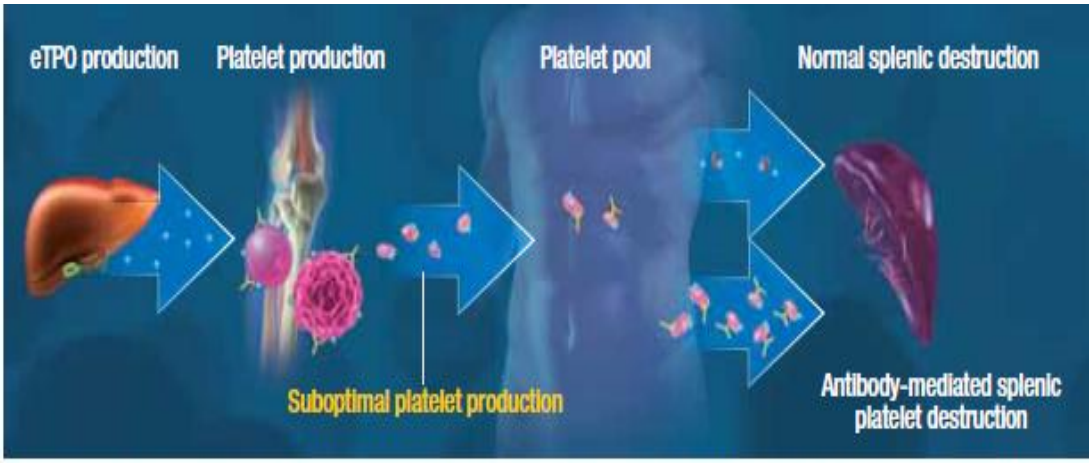
thrombocytopenia through a reduction in platelet lifespan. This mechanism results in lower TPO concentrations in patients with ITP when compared to those with aplastic anemia exhibiting similar platelet counts.



In ITP, antibodies bind to glycoproteins on healthy circulating platelets



Antibody-coated platelets are recognised by macrophages primarily in the spleen leading to their destruction



Fewer megakaryocytes and an inappropriately low endogenous thrombopoietin level result in suboptimal platelet production

Figure (2) Current view of ITP – increased platelet destruction and suboptimal platelet production

V-Diagnosis:

Recommendations for diagnosis of primary ITP in children and adults:

The diagnosis of ITP is based principally on the exclusion of other causes of isolated thrombocytopenia using patient history, physical examination, blood count, and evaluation of the peripheral blood film (to exclude other hematological conditions, including hereditary thrombocytopenia and pseudothrombocytopenia). If therapy is administered, platelet count should be closely monitored for response as a diagnostic aid.

A complete history, physical examination, full blood count, and an expert analysis of the peripheral blood film should be evaluated at initial diagnosis (Grade C recommendation). Based on the evidence currently available, when there is isolated thrombocytopenia and no abnormal features present on physical examination or examination of the blood smear, a bone marrow examination is not required in the initial diagnosis (Grade B recommendation), whether or not treatment is recommended.

The detection of Helicobacter pylori infection, using the urea breath test or the stool antigen test, should be included in the initial work-up in appropriate geographical areas (evidence level IIa; Grade B recommendation).

The majority of authors routinely test for hepatitis B virus (HBV), HIV, and hepatitis C virus (HCV) in all adult patients (evidence level IIb).

Quantitative immunoglobulin (Ig) level testing is indicated to exclude immune deficiency syndrome (evidence level IV; Grade C recommendation) or before treatment with IVIg. In children, Ig level testing may be considered at baseline and should be measured in those children with persistent or chronic ITP as part of a reassessment evaluation.

Bone marrow examination could be appropriate in those relapsing after remission, in patients not responding to initial treatment options, where splenectomy is considered, or if other abnormalities are detected in the blood count or morphology (evidence level III; Grade C recommendation). This examination should ideally include an aspirate, biopsy, flow cytometry, and cytogenetics (evidence level IV; Grade C recommendation).

Patient history:

The evaluation of thrombocytopenia requires a thorough assessment of its differential diagnosis, which may include factors such as alcohol abuse, infections, medications, liver disease, and primary hematologic disorders, as outlined in **Table 1**. Additionally, secondary causes of immune thrombocytopenic purpura (ITP) should be thoroughly examined. Research indicates that 55% of pediatric ITP cases have a history of previous infections and that there is an elevated risk of ITP associated with measles-mumps-rubella vaccination in children [(15)].

Table (1) Differential diagnoses of thrombocytopenia

Previously diagnosed or possible high risk for conditions that may be associated with immune thrombocytopenia (e.g., infections [HIV, HCV, HBV]), autoimmune/immunodeficiency disorders (CVID, systemic lupus erythematosus, or APS), and malignancy (e.g., lymphoproliferative disorders)
Liver disease (including cirrhosis or portal hypertension)
Splenomegaly
Drugs (prescription or nonprescription), including heparin, alemtuzumab, PD-1 inhibitors, abciximab, valproate, alcohol abuse, consumption of quinine (tonic water), exposure to environmental toxins, or chemotherapy

Bone marrow diseases, including myelodysplastic syndromes, leukemias, other malignancies, metastatic disease, myelofibrosis, aplastic anemia, megaloblastic anemia, myelophthisis, and Gaucher disease
Recent transfusions (rare possibility of posttransfusion purpura) and recent vaccinations
Inherited thrombocytopenia: TAR syndrome, radioulnar synostosis, congenital amegakaryocytic thrombocytopenia, Wiskott-Aldrich syndrome, MYH9-related disease, Bernard-Soulier syndrome, type IIB VWD, or platelet-type VWD
Other thrombocytopenic disorders (DIC, TTP, HUS, Evans syndrome)

Physical examination findings are typically normal except for signs of bleeding. The presence of moderate or severe splenomegaly could indicate an alternative etiology. Symptoms such as fever, weight loss, hepatomegaly, splenomegaly, or lymphadenopathy may suggest an underlying condition like HIV, chronic liver disease, systemic lupus erythematosus (SLE), lysosomal storage disorders, or lymphoproliferative diseases.

Laboratory investigations

- ***Peripheral blood count***

The complete blood count (CBC) typically appears normal, aside from isolated thrombocytopenia. If microcytic anemia is observed due to blood loss, its severity should correspond with the volume and duration of the bleeding and may suggest iron deficiency (evidence level IV). The reticulocyte count can help determine the underlying cause of anemia. Additionally, significant deficiencies in vitamin B12 and folate may lead to thrombocytopenia [(16)].

- ***Evaluation of peripheral blood smear***

A qualified hematologist or pathologist should examine a peripheral blood smear. It is important to rule out pseudothrombocytopenia caused by EDTA-dependent platelet agglutination (evidence level III). The blood smear may reveal abnormalities that are not typical of immune thrombocytopenic purpura (ITP), such as schistocytes found in thrombotic thrombocytopenic purpura or hemolytic uremic syndrome, as well as leukocyte inclusion bodies associated with myosin heavy chain 9–related disease. An abundance of giant or small platelets may suggest an inherited form of thrombocytopenia[(17)].

- ***Bone marrow examination***

Bone marrow examination can provide valuable insights for patients experiencing systemic symptoms, exhibiting abnormal signs, or when there is a suspicion of an alternative diagnosis. This procedure may be conducted while considering splenectomy or prior to initiating a new treatment [(18)]. When carried out, the bone marrow examination should encompass an aspirate, biopsy, flow cytometry, and cytogenetic analysis (evidence level IIb-IV) to differentiate immune thrombocytopenic purpura (ITP) from lymphoproliferative disorders, myelodysplastic syndromes, or primary bone marrow diseases [(19)]. For elderly patients or those who do not respond to corticosteroids or intravenous immunoglobulin, next-generation sequencing (NGS) panels should be utilized to evaluate genes linked to clonal malignancies. It is important to note that roughly one-third of ITP patients exhibit increased reticulin in the bone marrow; however, this finding does not relate to the severity of the disease, clinical characteristics, or existing comorbidities, and should not undermine the diagnosis unless there are substantial amounts of type I collagen detected in the trichrome stain (evidence level III) [(20)].

Prognosis:

The results of Immune Thrombocytopenic Purpura (ITP) can vary significantly from person to person, making it difficult to foresee the progression of the condition. Adults are more prone to develop chronic ITP, and instances of spontaneous recovery are rare. Nevertheless, many adults with ITP may have a mild and stable form of the disease that does not require treatment. In contrast, ITP typically presents as an acute condition in children, especially those under the age of 10, with most cases showing improvement even after several weeks or months of severe low platelet counts. Approximately 80% of children will recover spontaneously within six months, regardless of whether they receive treatment. About 15–20% of children, however, may go on to develop chronic ITP.

Among ITP patients who respond to therapy, mortality is similar to that of the general population. Among those who do not respond within the first few years of receiving therapy, there is a higher risk of morbidity and mortality. Deaths are rare, but may be as high as 3% per year in refractory ITP patients and are usually related to intracranial hemorrhage or infection.

Treatment of patients with immune thrombocytopenia:

Table (2) Therapies for the treatment of ITP

Clinical situation	**Therapy option**
Initial treatment of newly diagnosed ITP	***Corticosteroids***
	Dexamethasone
	Methylprednisolone
	Prednisolone
	IVIG
	Anti-D
Subsequent treatment	***Medical therapies***
	Medical therapies with robust evidence
	Rituximab
	TPO-RAs: eltrombopag, avatrombopag, romiplostim
	Fostamatinib
	Medical therapies with less robust evidence
	Azathioprine
	Cyclophosphamide
	Cyclosporine A
	Danazol
	Dapsone
	Mycophenolate mofetil
	TPO-RA switch
	Vinca alkaloids
	Surgical therapies
	Splenectomy
	Accessory splenectomy

Treatment of patients failing multiple therapies	Alemtuzumab
	Combination of initial and subsequent therapies
	Combination chemotherapy
	Clinical trials
	HSCT
	Splenectomy, if not already performed
	Supportive care

Who should be treated?

Treatment should always be customized according to the individual patient, as numerous factors influence treatment choices. Key elements that affect management decisions include the severity of bleeding, the patient's age, pre-existing conditions that might increase the risk of bleeding, potential complications from certain therapies, lifestyle and activity levels, fatigue (refer to "Quality of Life of Adults with ITP"), tolerance to side effects, the necessity of interventions that pose a bleeding risk, availability of care, patient expectations, levels of worry or anxiety, and the need for non-ITP medications that might also increase bleeding risk. Factors such as being female, use of nonsteroidal anti-inflammatory drugs (NSAIDs), having a platelet count below 20 × 10^9/L, and the use of anticoagulant medications are all linked to the occurrence of bleeding at diagnosis. Both bleeding and infections significantly contribute to mortality rates. While the risk of bleeding is not typically associated with any specific threshold platelet count, it tends to rise when the count drops below 20 × 109/L. Considering this information and the authors' agreement, treatment is generally not recommended for patients with platelet counts above 20 × 109/L, unless there are specific conditions involving bleeding due to platelet dysfunction or other known or unknown issues with hemostasis, trauma, surgery, clearly defined comorbidities that enhance bleeding risk, necessary antiplatelet or anticoagulation therapies, or non-hemorrhagic complications like fatigue associated with ITP, especially in individuals whose jobs or lifestyles expose them to potential injuries. It is essential to take patient preferences into account when evaluating treatment possibilities [(21)].

Alongside treatment tailored to the individual patient and the specific phase of their disease, it is essential to educate patients about the clinical objectives of their treatment and provide reassurance, enabling them to maintain their normal activities. The primary clinical goals include resolving any bleeding occurrences or preventing significant bleeding by ensuring proper hemostasis. It is important to aim for a platelet count of at least 20 to 30 × 10^9/L; however, achieving a normal platelet count is not necessary. This threshold may not be suitable for active patients or those over 60 years old, as studies have indicated higher instances of bleeding, thrombosis, and mortality in individuals in this age group, as well as those with other health issues or those taking anticoagulants. Treatment response should guide the selection of any additional therapies, with an emphasis on minimizing side effects while assessing the need for further interventions. Additionally, patients' feelings of fatigue should be taken seriously unless they are exacerbated by treatment-related toxicity (for further details on fatigue's effects, refer to "Quality of life of adults with ITP"). ITP therapy can typically be administered on an outpatient basis, except in situations involving active bleeding, specific medical considerations (such as anticoagulant therapy), the need for close observation, or if it is the initial diagnosis of thrombocytopenia and the platelet count is low ≤ 20 × 109/L [(22,24)].

Initial treatment of newly diagnosed patients:

Corticosteroids are the standard initial treatment for adults with ITP who need treatment and do not have a relative contraindiction: prednisolone at 1 mg/kg (maximum dose 80 mg, even in patients weighing >80 kg) for 2 weeks, to a maximum of 3 weeks, or dexamethasone 40 mg/d for 4 days, repeated up to 3 times.

Corticosteroid therapy

Corticosteroids continue to be the primary first-line treatment for patients who have just been diagnosed and should only be administered for a short duration. These medications provide several advantageous effects on platelet hemostasis by lowering the rate of platelet clearance and enhancing platelet production. Furthermore, they may help decrease bleeding, regardless of any increase in platelet numbers, due to a direct impact on blood vessels. While the consensus panel noted that certain patients could sustain a platelet response with a daily prednisolone dose of 5 mg or less, the long-term side effects associated with corticosteroids outweigh their benefits [25].

IVIg

The most common treatment schedule for IVIg in children with newly diagnosed ITP is 0.8 to 1 g/kg in a single dose [26], but some studies continue to use 0.4 g/kg per day over 5 days [27]. It is often combined with steroids, antihistamines, and paracetamol to reduce side effects, especially headaches. Treatment is usually discontinued once a safe platelet count is reached, although it can be repeated as needed. In severe bleeding, a second dose of IVIg (0.8 to 1 g/kg) is often given if there has been no initial response to the first dose. Increased platelet count with IVIg has been reported in over 80% of children with ITP (evidence level Ib-IIb) [28]. Four studies have compared IVIg with anti-D in children newly diagnosed with ITP; three studies reported no significant difference, and one study reported improved efficacy with IVIg (evidence level Ib-IIb) [29].

The phase 3 TIKI trial compared single-dose IVIg (0.8 g/kg) with observation in children with newly diagnosed ITP, platelet count ≤20 × 109/L, and grade 1-3 bleeding (evidence level Ib). Overall and complete response rates were significantly higher with IVIg vs observation at 1 week and 1 month, at 3 months only the complete response rate was significantly higher, and at 6 and 12 months there was no significant difference in either measure. The rate of chronic ITP development did not differ significantly between the two groups (approximately 10% in each group). [28].

IV anti-D

Anti-D can be given to Rh(D)-positive children as a short infusion, and it is usually effective in transiently increasing platelet counts [27]. Four studies since 2010 have evaluated the treatment efficacy of anti-D in newly diagnosed children with ITP and compared it with IVIg, methylprednisolone, or both [30].

Treatment options for children with persistent or chronic ITP

1. Most children can be managed with watchful waiting, as described (see “Expectant watch-and-wait policy”; Grade C recommendation).

4. Multiple pediatric studies support the use of TPO-RAs in children with persistent or chronic ITP, demonstrating good response and reduction in bleeding frequency with an absence of side effects in the majority of patients (evidence level Ib; Grade A recommendation).

Studies have indicated that older age, higher platelet counts, and absence of preceding infections are risk factors for chronic ITP (evidence levels IIb, III). Less established risk factors for chronicity include female sex and a decrease in Ig (evidence level III). A recent registry analysis found no association between platelet count at diagnosis and ITP remission at 12 or 24 months. Spontaneous remission may occur at any time, even >3 years from diagnosis [31].

Many children stabilize with an adequate platelet count (>20-30 × 109/L), have no symptoms unless injured, and do not benefit from restrictions in their activity. There may be ongoing vulnerability to excessive bleeding following trauma; it is advisable for the family to carry a card or letter or for the child to wear a bracelet with details of the disorder and contact information in case of emergency. The role of puberty in this process remains uncertain. The onset of menstruation may be problematic and can be managed with antifibrinolytic agents and/or hormonal medication [32].

Treatment of children with persistent/chronic ITP

A. Dexamethasone, high-dose methylprednisolone, IVIg/anti-D.

B. TPO-RAs.

Eltrombopag and romiplostim have been studied extensively in children, leading to FDA and European Medicines Agency licenses in children ≥ 1 year old with ITP for > 6 months' duration with insufficient response to corticosteroids, Igs, or splenectomy. In general, TPO-RAs should be used as preferred treatment in patients with ITP in whom alleviating the thrombocytopenia is likely to provide a clear clinical benefit, including reducing the risk of bleeding and/or improving the HRQoL. The lowest dose required to achieve and maintain a platelet count ≥ 50 × 109/L should be used for eltrombopag and romiplostim. PROMACTA® (eltrombopag) for oral suspension [prescribing information]. East Hanover, NJ: Novartis Pharmaceuticals Corporation; 2018

The PETIT and PETIT2 studies investigating eltrombopag in children with chronic immune thrombocytopenic purpura (ITP) indicated that around 80% of patients achieved a platelet count of ≥50 × 109/L at least once (evidence level Ib). In the PETIT2 study, 40% of the participants maintained a platelet count of ≥50 × 109/L for a minimum of 6 weeks without the need for rescue treatment. Neither trial reported any instances of World Health Organization grade 3 or 4 bleeding among patients treated with eltrombopag. In the PETIT trial, 30% of the children received the maximum dose of eltrombopag (75 mg/day), while 89% of the participants needed at least one dose adjustment. The median time to achieve a response was between 12 to 20 days, depending on the patients' ages. [33]. There are few data on the administration of eltrombopag for > 1 year in children.

C- Romiplostim.

For children, the suggested starting dosage is 1 μg/kg per week, given through subcutaneous injection. This dosage can be modified based on the platelet count levels. A phase 3 study that lasted for 24 weeks found a median average dose of 3.9 μg/kg (with an interquartile range from 2.4 to 7.3) and reported a median most commonly used dose of 5.5 μg/kg (interquartile range, 3 to 10) during the last 8 weeks. If there is no risk of thrombosis, the authors recommend beginning with a dose of 3 μg/kg per week [34]. Research on the use of romiplostim in pediatric patients with ITP, both newly diagnosed and chronic cases, has indicated overall response rates ranging from 71% to 88%, with a median response time of 4 to 5 weeks (evidence levels Ib-III) [34]. A study of long-term romiplostim treatment in children found AEs and platelet responses similar to those seen in adult patients and maintenance of effect over 4 years [33]. However, another study with 24 weeks of romiplostim treatment reported no sustained response (platelet count ≥50 × 109/L for ≥6 months with no ITP medication) following romiplostim discontinuation (evidence level Ib) [34].

C- *Rituximab*.

Splenectomy in ITP can achieve high and durable response rates. Since 2010, studies that included adults, as well as children/adolescents, reported initial response rates of 83% to 97% (evidence levels IIb-III), decreasing to 59% after a median 20 year (range, 10-43) follow-up. Firm conclusions on splenectomy in children cannot be drawn from the current literature, because studies do not separate results by age or disease duration [35].

Quality of life and daily activities

The impact of ITP, especially chronic ITP, on patient HRQoL is substantial (evidence level III). The most difficult ITP symptom to treat is severe fatigue, reported in 39% to 59% of adult patients with ITP; yet, it is under-recognized by healthcare practitioners. ITP leads to impaired HRQoL across emotional, functional, reproductive, and health domains, and it impacts daily living, in turn affecting mental health [36,37].

Patient-reported outcomes and support of patients with ITP

The ITP IWG recommends a treatment goal of a safe platelet count in the absence of bleeding, not a normal platelet count [1]. Nevertheless, platelet counts remain a focus for health care practitioners, while fatigue and

mental health aspects are the major concerns of patients. ITP patient support services are provided in numerous countries, but continued increased awareness of the impact of ITP on HRQoL among health care professionals is required. International ITP Alliance. Global ITP support ambassadors. Available at: http://globalitp.org/index.php/patient-support. Accessed 15 October 2019.

Quality of life of children with ITP

HRQoL of children with newly diagnosed ITP improves on disease resolution (evidence level IIa; Grade B recommendation).

KIT, developed in 2007, is ITP specific and consists of child self-reporting (for children aged ≥7 years), parent proxy reporting, and assessment of parent impact [(38)]. The established, but non-ITP specific, Pediatric Quality of Life Inventory (PedsQL) questionnaire may also be used. HRQoL is harder to assess in children than in adults; irritability or depression may be observed instead of fatigue.

Normal attendance and play at kindergarten, school, or college, depending on age, is essential. The risk of bleeding and information about ITP should be provided to the school in a way that facilitates inclusion, not isolation (Grade C recommendation).

Active participation in low-risk activities should be maintained, irrespective of platelet count and treatment (Grade C recommendation).

Conclusion

The reviewed literature highlights the importance of integrating clinical findings with immune mechanisms and individualized assessment. Further studies are needed to clarify the clinical implications of the described observations.

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