International Journal of Allied Medical Sciences and Clinical Research (IJAMSCR)

ISSN:2347-6567

IJAMSCR |Volume 11 | Issue 3 | July - Sept - 2023
www.ijamscr.com

Research article *Medical research*

Idiopathic thrombocytopenic purpura-a literature based review

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Published on: September 6, 2023
doi : https://doi.org/10.61096/ijamscr.v11.iss3.2023.316-324

ABSTRACT

Immune thrombocytopenia (ITP) is a syndrome in which platelets become coated with autoantibodies to platelet membrane antigens, resulting in splenic sequestration and phagocytosis by mononuclear macrophages. Immune thrombocytopenic purpura (ITP) is an autoimmune pathology characterized by a low platelet count, purpura, and hemorrhagic episodes caused by antiplatelet autoantibodies. The exclusion typically makes the diagnosis of the known causes of thrombocytopenia. IgG autoantibodies sensitize the circulating platelets. It leads to the accelerated removal of these cells by antigen-presenting cells (macrophages) of the spleen and sometimes the liver or other components of the monocyte-macrophage system. 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. Certain drugs can also cause immune thrombocytopenia indistinguishable from ITP. The clinical presentation may be acute with severe bleeding, or insidious with slow development with mild or no symptoms. The initial laboratory tests useful at the first visit to predict future diagnosis were erythrocyte count, leukocyte count, anti-glycoprotein (GP) IIb/IIIa antibodies, reticulated platelets, plasma thrombopoietin level. Treatment should be restricted to those patients with moderate or severe thrombocytopenia who are bleeding or at risk of bleeding. It should be limited in duration unless demonstrated that symptomatic thrombocytopenia persists. Patients with mild, asymptomatic thrombocytopenia, discovered incidentally on a routine blood count, should not be treated. We present a case report on ITP and summarize the key points in the diagnosis and management of ITP. An optimized treatment strategy should aim at elevating the platelet counts to a safety level with minimal toxicity and improving patient health-related quality of life, and always needs to be tailored to the patients and disease phases. In this review, we address the concepts of adult ITP diagnosis and management and provide a comprehensive overview of current therapeutic strategies under general and specific situations.

Keywords: Romiplostim, immune thrombocytopenia, autoimmune disease, platelets, histopathology, rituximab.

INTRODUCTION

Immune thrombocytopenic purpura (ITP) is an autoimmune disease characterized by a low platelet count, purpura, and hemorrhagic episodes caused by antiplatelet autoantibodies. The diagnosis is typically made by excluding the known causes of thrombocytopenia. IgG autoantibodies sensitize the circulating platelets. It leads to the accelerated removal of these cells by antigen-presenting cells (macrophages) of the spleen and sometimes the liver or other components of the monocyte-macrophage system. The bone marrow compensates for platelet destruction by increasing platelet production. ITP most often occurs in healthy children and young adults within a few weeks following a viral infection. Thrombotic thrombocytopenic purpura (TTP) is a rare thrombotic microangiopathy caused by an acquired autoantibody that leads to decreased activity of the von Willebrand factor-cleaving protease ADAMTS13 that results in hemolytic anemia and severe thrombocytopenia. While the treatment courses for both ITP and TTP may include corticosteroids and rituximab, a key treatment difference is urgent therapeutic plasma exchange (TPE) for all patients with TTP, whereas TPE is not effective for ITP.

ITP is usually manageable with immunosuppressive therapy. An identical form of autoimmune thrombocytopenia can also

be associated with chronic lymphocytic leukemia, lymphomas, SLE, infectious mononucleosis, and other bacterial and viral infections. Certain drugs can also cause immune thrombocytopenia indistinguishable from ITP. Most children have spontaneous remission within a few weeks or months, and splenectomy is rarely needed. However, young adults rarely have spontaneous remissions necessitating splenectomy within the first few months after diagnosis.

Epidemiology

The annual incidence is estimated at between 1/25,600-37,000 in Europe, with a female to male ratio of 1.3:1. Although immune thrombocytopenia (ITP) can occur at any age, incidence shows an age-specific bimodal distribution for men with two incidence peaks observed in boys (under 18 years old) and among those older than 60 years of age.

Immune thrombocytopenic purpura can be divided into two classifications; acute and chronic. The acute form presents in childhood, affects both sexes, and may be prefaced by a viral infection. Most children (85%) have a benign course and do not require treatment. They can spontaneously recover within three months. The chronic form affects individuals between ages 20 to 50 years; there is a female/male ratio of 3 to 1, and it is usually not preceded by a viral infection. The female preponderance is thought to have some relationship to the increased prevalence of autoimmune disease in women. It may present with bleeding episodes for months or years; during that time, the platelet counts are close to normal. Fewer than 10% of children develop chronic ITP.

Etiology

The etiology is unknown. However, the disease origin is not genetic as familial cases are exceptional. Platelet destruction, mediated by autoantibodies mainly in the spleen, is associated both with impaired platelet production and with T-cell-mediated effects.

Immune thrombocytopenic purpura can occur with infections (e.g., human immunodeficiency virus), malignancy (e.g., adenocarcinoma and lymphoma), and common variable immunodeficiency and autoimmune diseases (e.g., systemic lupus erythematosus, autoimmune hepatitis, and thyroid disease).

In these diseases, anti-platelet antibodies form, leading to platelet destruction. Drugs such as acetazolamide, aspirin, aminosalicylic acid, carbamazepine, cephalothin, digitoxin, phenytoin, meprobamate, methyldopa, quinidine, rifampin, and sulfamethazine may also cause autoimmune thrombocytopenia, autoantibody production against platelets is advocated as one etiology for ITP. The modern theory also considers the possibility of a failure of the self-tolerance mechanism.

Pathophysiology

The spleen is an important site of autoantibody production. Sequestration of anti-platelet IgG antibodies occurs in the spleen's red pulp, where sensitized platelet removal occurs by phagocytosis. Research showed that radiolabeled-IgG sensitized platelet removal occurs in a few hours compared with a normal platelet half-life of 8 to 9 days.

In contrast to maternal ITP, gestational thrombocytopenia rarely brings the count below 70,000 /dL, typically does not cause bleeding, and has its origins in a dilutional, not consumptive, mechanism.

Neonatal alloimmune thrombocytopenia may occur in pregnant women who are negative for the platelet antigen PL a1 but were sensitized in prior pregnancies by infants who were PL a1 positive or by blood transfusion. The condition has also involved other platelet antigens. Pregnant women with ITP have an increased incidence of fetal loss, a low fetal birth rate, and a higher incidence of premature births.

In drug-induced ITP, the drug absorbs the platelet cell membrane. The immune system makes antibodies to the target drug-platelet complex, which results in the removal of the sensitized platelet by phagocytes residing in the spleen and liver. The activation of the complement system by the classical pathway is another effector mechanism of platelet cell damage (thrombocytopenia).

Childhood immune thrombocytopenic purpura often occurs within a few weeks following a viral infection, suggesting a possible cross-immunization between viral and platelet antigens, the absorption of immune complexes, or a hapten mechanism

Many other platelet antigens are a target of autoantibodies, including GPIIb/IIIA and GP V (after chickenpox). However, their exact role in diagnostic testing is dubious at best.

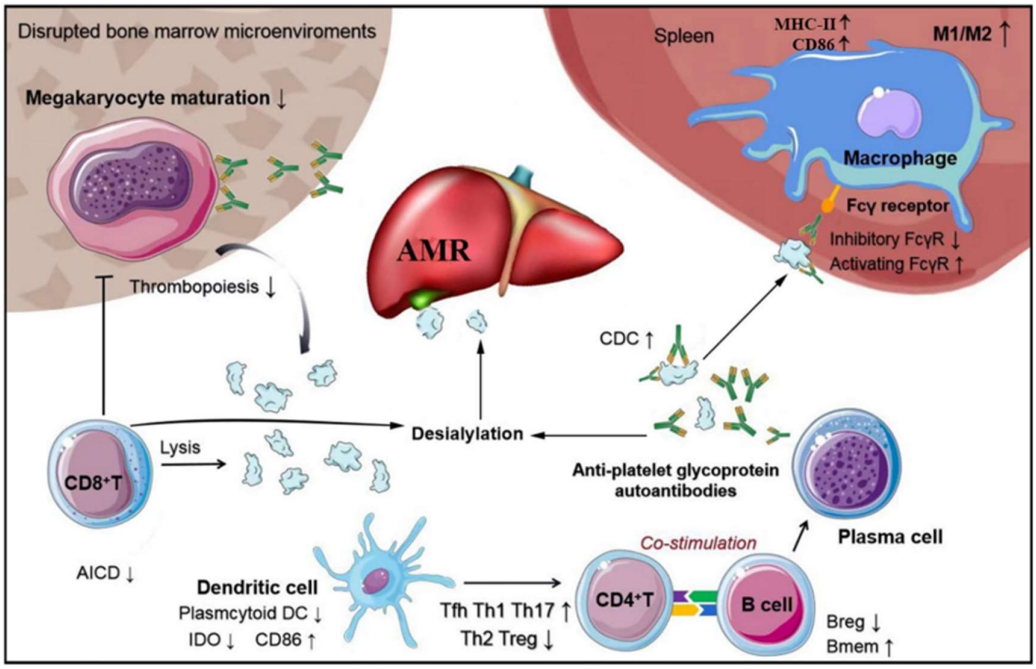


Fig 1: Pathophysiology of ITP

Thrombocytopenia in ITP is the result of both increased platelet destruction and suppressed platelet production. Platelet autoantigens are abnormally recognized, processed, and presented by DCs, and then CD4+ T helper cells are activated toward a proinflammatory profile, which dictate the differentiation of B cells into autoantibody-secreting plasma cells. Autoantibodies not only mediate platelet phagocytosis by macrophages through Fcγ receptors (FcγRs) but also induce platelet desialylation and subsequent clearance through hepatocyte Ashwell–Morell receptors (AMRs). Splenic macrophages have increased expression of major histocompatibility complex (MHC)-II and CD86 and can also present autoantigens to Th cells. CD8+ cytotoxic T lymphocytes (CTLs) can directly lyse platelets or induce platelet apoptosis. Moreover, autoantibodies and CTLs interfere with megakaryocyte maturation and apoptosis, leading to decreased platelet production in ITP. AMR Ashwell–Morell receptor, FcγR Fcγ receptor, M1/M2 M1/M2 macrophage polarization, CDC complement-dependent cytotoxicity, AICD activation-induced cell death, DC dendritic cell, IDO indoleamine 2,3-dioxygenase, Tfh follicular T helper cell, Th T helper cell, Treg regulatory T cell, Breg regulatory B cell, Bmem memory B cell, MHC-II major histocompatibility complex-II, ↓ means decreased or downregulated, ↑ means increased or upregulated.

Histopathology

Histopathology of immune thrombocytopenic purpura can often reveal the increased production of megakaryocytes in the bone marrow. This finding suggests that thrombocytopenia is secondary to increased platelet destruction rather than decreased platelet formation. Harrington and coworkers first showed in 1951 that the plasma from a patient with immune thrombocytopenic purpura caused thrombocytopenia when transfused into a healthy subject.

Role of B cells

Autoreactive B lymphocytes secrete antiplatelet antibodies atho genesis. The most commonly occurring autoantibodies (~75%) in patients with ITP are directed against the platelet surface glycoprotein (gp) complexes gpIIb–IIIa and gpIb–IX. Antibodies against other glycoproteins (Ia–IIa, IV, and V) have been identified, and multiple platelet antigen specificities can be found in most patients. Although antibodies are primarily of the IgG subtype, IgM and IgA may be found. Platelets are targeted by the attachment of autoantibodies to their surface gp antigens, bound to Fcγ receptors expressed on tissue macrophages of the reticuloendothelial system and cleared from the circulation. Gamma camera imaging of ITP patients injected with ^{111}In-labeled autologous platelets revealed that uptake occurs primarily in the spleen and liver. Complement-induced lysis following antibody binding may also play a role After platelet internalization and degradation, macrophages express platelet epitopes on their surface and secrete cytokines that stimulate initiating CD4$^+$ T-cell clones and clones with additional specificities. Unique to patients with ITP, autoreactive CD4$^+$ T cells recognize several distinct epitopes on gpIIb–IIIa, leading to autoimmune response expansion and accelerated platelet destruction. The trigger for the initiating autoantibody response is unknown, although autoreactive T helper (Th) cells that interact with antibody-producing B cells are required.

Platelet-associated autoantibodies are detected in 50%–70% of patients with ITP, emphasizing the limitations of the currently available assays and/or suggesting that other or additional mechanisms are involved. A quantitative assay for nonspecific platelet-associated IgG had a positive predictive value of only 46% in patients with ITP and it could be detected in disease states other than ITP, including hematologic malignancy and infection. Assays for antibodies targeting gpIIb–IIIa, gpIb–IX, and gpIIa–IIIa may be more

specific, but have limited sensitivity, and the diagnosis remains dependent on clinical presentation for the people.

Multi-dysfunctional pathophysiology in ITP

Cytotoxic lymphocytes appear to be abnormally activated by autoreactive lymphocyte clones. $CD3^+$ lymphocytes from patients with ITP show increased expression of cytotoxic genes such as tumor necrosis factor α, perforin, and granzyme A and granzyme B. Platelets from patients with active ITP displayed in vitro lysis when incubated with $CD3^+CD8^+$ T effector cells but not with $CD3^-CD16^+CD56^+$ natural killer (NK) cells. Killer cell immunoglobulin like receptor (KIR) genes showed increased expression, and $CD3^+$ lymphocytes expressing KIRs were greater in number in ITP patients in remission than in patients with active ITP or normal controls. The KIR family of genes downregulate cytotoxic T-lymphocyte and NK cell responses, preventing lysis of target cells. Megakaryocytes may also be damaged in ITP by autologous $CD8^+$ T cells. These findings suggest that cytotoxic T cells play a part in at least some patients with ITP, and down regulation of the auto-T-cell response is a potentially effective therapeutic strategy.

Symptoms

Immune thrombocytopenia might not have symptoms. When symptoms occur, they might include:

Petechiae

Bleeding into the skin looks like tiny reddish-purple spots, also known as petechiae. Petechiae might look like a Srash. Here they appear on a leg (A) and on the stomach area (B).



Fig 2: Petechiae

- Easy bruising.
- Bleeding into the skin that looks like tiny reddish-purple spots, also known as petechiae. The spots mostly show up on the lower legs. They look like a rash.
- Bleeding into the skin that's larger than petechiae, also known as purpura.
- Bleeding from the gums or nose.
- Blood in urine or stools.
- Heavy menstrual flow.

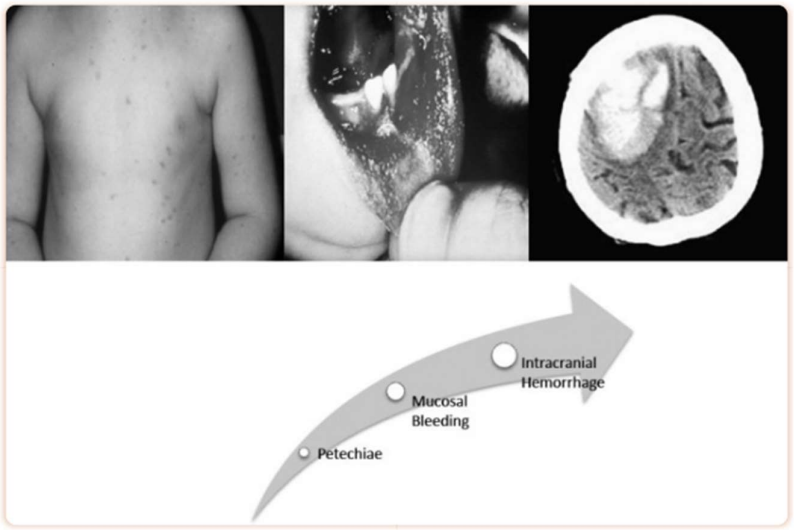


Fig 3: Clinical manifestations of immune thrombocytopenic purpura in increasing order of severit

Factors that frequently precede symptoms of ITP include:

- Illness, especially viral infections such as hepatitis C and AIDS
- Fevers
- Dehydration
- Trauma
- Medications, such as aspirin or ibuprofen
- Pregnancy
- Autoimmune conditions such as lupus and primary Sjogren's syndrome
- Slow-growing lymphomas and leukemias

Diagnosis

Diagnosis of ITP is made using a combination of methods. If you have symptoms, your healthcare provider will discuss your medical history with you. You will also have a physical examination, which includes an examination of your skin, heart, and lungs.

Blood smear

You are likely to have diagnostic blood tests as part of your evaluation. Blood tests include a complete blood count (CBC) and electrolyte levels. A CBC provides a platelet count. Typically, there are low numbers of platelets in idiopathic thrombocytopenic purpura. White blood cells (WBCs), red blood cells (RBCs), and electrolyte levels tend to be normal in ITP.

Bone marrow aspiration

Examines platelet production and rules out any aberrant cells that the marrow may be producing that might affect platelet counts.

Emerging therapies target platelet production

The currently available treatment for ITP targets the autoimmune response and platelet destruction. Various treatment options, such as corticosteroids, androgens, cytotoxic chemotherapy, rituximab, immunosuppressive agents, and immunoglobulin preparations, are directed against different steps and phases of the immune response. Therapies targeting dysregulated T or B lymphocytes, including etanercept, anti-CD40 ligand, and mycophenolate mofetil, have shown activity in initial studies in patients with refractory ITP. Decreased platelet production and TPO (thrombopoietins) levels within the normal range despite thrombocytopenia in patients with ITP suggest an opportunity to stimulate platelet production as a treatment approach. Several candidate molecules have been investigated including recombinant TPO preparations and TPO receptor agonists.

Treatment

A sound understanding of pathophysiology is essential for the appropriate management of ITP in children. Rapid strides in pharmacotherapy have added to the pre-existing predicament of when to treat and how to treat. Clinicians must clearly understand that no study has shown that any form of treatment decreases mortality or alters the risk of the disease process becoming chronic. Personalization of treatment based on platelet count, age, clinical picture, duration, lifestyle issues, economic considerations, and parental, patient, or physician concerns is the best approach. A standard treatment protocol for all ITPs would be a step backward.

Treatment of ITP can be divided into medical and surgical management. Medical management is further divided into first-line and second-line pharmacotherapy. Supportive therapy by a team experienced in the variable course and outcome of ITP is crucial. Education of the patient, teachers, siblings, parents, and primary care physician of the need for close monitoring for any acute bleed, especially intracranial or intra-abdominal, can significantly decrease mortality and morbidity. The child and family also require psychosocial support and trauma prevention advice, including a strong warning about participating in contact sports.

Medical options for front-line drug therapy are corticosteroids, intravenous (IV) immunoglobulin (Ig), and IV Rh anti-D.

Corticosteroids

Sartorius in 1984 was the first to report the benefit of prednisolone in ITP. Another study by Buchanan and Holtkamp in the same year reaffirmed that prednisolone boosts platelet counts by day 7 of treatment. A well-established consensus exists regarding the initial benefit from oral prednisolone. Corticosteroids act by impairing the clearance of opsonized platelets in bone marrow and peripheral organs and reducing autoantibody levels in the body. Many prospective, randomized studies confirm that corticosteroids increase platelet levels more rapidly than no treatment. High-dose prednisone at approximately 4 mg/kg/d for 4 days or the shortest period possible can minimize side effects as well as maintain the therapeutic significance in treatment of ITP. Treatment duration and drug dose are determined by the response and side effects. Some of the common complications associated with corticosteroid treatment are avascular necrosis, diabetes, gastritis, ulcers, growth retardation, hypertension, insomnia, osteoporosis (in adults), personality changes, and opportunistic infections. Tapering the dose and terminating the drug on either stoppage of bleeding or on achieving a platelet count higher than 20×10^9/L are important. In fact, many doctors stop treatment after 2-3 weeks regardless of the response.

Intravenous immunoglobulin

Imbach et al were the first to propose the role of IV IgG in the reversal of thrombocytopenia. IV IgG acts by impairing the clearance of opsonized platelets, probably mediated through the FcγRIIb receptor. Some studies also suggest that IV IgG might cause increased clearance of antiplatelet antibodies via saturation of the neonatal Fc salvage receptor for IgG. Our present knowledge of IV IgG is mostly informed by 2 Canadian clinical trials. These studies concluded that IV IgG had a faster response rate compared to corticosteroids when the target platelet count was 50×10^9/L. Also, they found that single-dose IV IgG of 0.8 g/kg was as effective as and safer than the larger dose of 1 g/kg for 2 days. IV IgG worked better than IV Rh anti-D to achieve a 20×10^9/L platelet count. IV IgG, although more expensive than IV Rh anti-D, is definitely one of the safer options available and may shorten the length of the hospital stay because of the drug's rapid response, usually within 24-48 h.

Some common infusion-related side effects are headache, fever, chills, and nausea. Other worrisome but rare side

effects include aseptic meningitis, renal impairment or failure, and thromboembolic events. The limitation of using IV RhIG is the lack of efficacy in Rh(D)-negative or splenectomized patients. Also, IV RhIG may induce immune hemolysis (immune hemolytic anemia) in Rh(D)-positive persons, which is the most common adverse effect, and should not be used when the hemoglobin concentration is less than 8 g/dL. Sporadic cases of massive intravascular hemolysis disseminated intravascular coagulation (particularly in elderly individuals), and renal failure have been reported. The treatment of chronic, refractory ITP may introduce risks of toxicity from medications that are comparable in severity to the risks of untreated thrombocytopenia. These treatments also may impact adversely on the patient's quality of life.

Other combination regimens that have been tested in RCTs for the initial management of ITP include mycophenolate mofetil (MMF) plus corticosteroids, all-trans retinoic acid (ATRA) plus HD-DXM, and oseltamivir plus HD-DXM. The open-label FLIGHT trial showed that MMF up to 1 g twice daily plus corticosteroids elicited a significantly higher complete response (CR) rate (91.5% vs. 63.9%) and fewer treatment failures (22% vs. 44%) than corticosteroid monotherapy. There was no difference in bleeding, rescue treatments, and severe adverse events between the 2 arms. However, MMF had an obvious detrimental effect on patient HRQoL. ATRA is an active derivative of vitamin A that has multiple immunomodulatory activities. Huang et al. observed in a phase II RCT that ATRA (10 mg twice daily for 12 weeks) plus HD-DXM induced a significantly higher SRR at 6 months than HD-DXM monotherapy (68% vs. 41%) in newly diagnosed ITP patients, and this novel combination treatment did not increase the occurrence of severe adverse events. With the recognition of desialylation-mediated platelet clearance in ITP pathogenesis, oseltamivir, a widely used anti-influenza sialidase inhibitor, was found to be the potential in ameliorating thrombocytopenia. Along similar lines, we conducted a multicenter RCT to assess the combination of oseltamivir (75 mg twice daily for 10 days) with HD-DXM versus HD-DXM alone as the initial treatment for ITP. It was encouraging that patients in the combination arm achieved a higher initial response rate (86% vs. 66%) and SRR at 6 months (53% vs. 30%) than those in the HD-DXM monotherapy arm; however, the superiority of response was gradually lost, and there was no statistical significance in SRR between the 2 arms after 1 year. The wide availability and affordability of ATRA and oseltamivir warrant further evaluation of these initial combination treatments in late-stage RCTs.

Splenectomy

Splenectomy remains the most effective therapy for corticosteroid-resistant or relapsed ITP patients by removing the major site of platelet phagocytosis and autoantibody production. Although splenectomy is becoming less preferred nowadays due to the availability of emerging non-surgical medications, it still offers the best chance for long-lasting remission, with an estimated durable response rate of 60–70%, even in TPO-RA and/or rituximab-resistant or relapsed patients. There is also evidence that even though CR was not achieved after splenectomy, most patients displayed a milder course of the disease and responded better to medical treatment. Most guidelines recommend deferring splenectomy for 12–24 months after diagnosis as some patients have a chance of spontaneous remission or stabilization of platelet count at a hemostatic level. Reconfirmation of the disease diagnosis is necessary before splenectomy, and under such circumstances, tests such as bone marrow evaluation, assays of anti-GP autoantibodies, and serum TPO levels are helpful. Laparoscopic splenectomy is as effective as open splenectomy for alleviating patient's thrombocytopenia, but it has lowered perioperative risks, shortened hospitalization, and decreased blood loss, thus becoming the standard procedure in most centers. To date, there is still a lack of reliable predictors of response to splenectomy. Autologous platelet scanning is capable of determining the predominant site of platelet sequestration, though not yet widely available.

Splenectomy is associated with a persistent 3–fourfold increase in the risk of venous thromboembolism (VTE) among ITP patients, and the risk remains elevated both early (< 90 days) and late (≥ 90 days) after splenectomy; therefore, postoperative thromboprophylaxis is appropriate in high-risk cases. There is also an increased risk of infection in splenectomized ITP patients, among whom the reported incidence of sepsis ranges from 2.1 to 6.0%. The necessity for antibiotic prophylaxis in splenectomized adult patients is still undetermined, and we suggest antibiotic prophylaxis in high-risk patients, such as immunocompromised cases, or those with a poor response to vaccination. Moreover, patients should be treated empirically with antibiotics at the first sign of infection. Vaccinations against encapsulated organisms (*Streptococcus pneumoniae*, *Neisseria meningitidis*, and *Haemophilus influenzae*) should be given ≥ 2 weeks before splenectomy and maintained. The incidence of surgical complications and mortality rates are relatively higher in patients > 60 years of age. Therefore, splenectomy should be considered a last resort and only be performed after a comprehensive assessment of the disease in elderly patients.

Thrombopoietin (TPO) mimetic agents

In order to move away from immune suppression, the first-generation TPO-mimetic drugs were developed in the 1990s including recombinant human TPO (rHu-TPO) and recombinant human megakaryocyte growth and development factor (rHu-MGDF). By stimulating the TPO receptor these agents raised the patients' platelet counts. However, although these TPO mimetics had good efficacy in ITP, antibodies were generated against the drugs in some patients.

Because the TPO mimetics were based on native endogenous human TPO, the antibodies against drugs were cross-reactive with native TPO resulting in profound thrombocytopenia. Development of the first generation TPO mimetics was therefore abandoned Over the last 20 years there has been significant drug development for ITP, beginning with the second generation thrombopoietin receptor agonists (TPO-RAs) This generation of TPO-RAs bears no resemblance to native thrombopoietin and therefore any antibodies directed against drug should not cross-react with the patient's native thrombopoietin. Romiplostim is a large peptibody molecule which binds to the same site as native TPO on the extracellular portion of the TPO receptor.

Eltrombopag is a small hydrazone molecule that binds to the transmembrane portion of the TPO receptor. Both drugs were launched in 2008 and have been used with great success in

primary immune thrombocytopenia as second-line agents. Their efficacy is high at around 80%.

More recently, another small molecule TPO receptor agonist has been developed, namely avatrombopag. This molecule binds to the same site as eltrombopag and stimulates the same pathway resulting in megakaryocyte proliferation and platelet production. All three approved TPO-RAs bind to the TPO receptor and stimulate the same pathway, shown in picture. These new TPO mimetics are well tolerated by patients and have avoided many patients being exposed to immune suppression or splenectomy.

Native TPO binds to the extracellular domain of the TPO receptor (left). After a change in configuration the JAK-STAT pathway is activated. TPO-RAs mimic native TPO by binding to the extracellular domain (romiplostim) or transmembrane region (eltrombopag and avatrombopag) of the TPO receptor.

Rituximab

Rituximab is a chimeric monoclonal antibody targeting CD20-expressing B cells. It has been commonly used as an off-label treatment for ITP for nearly 2 decades. The short-term response rates range from 60 to 70% in patients treated with the standard 4 weekly doses of 375 mg/m^2 rituximab, and the response is usually achieved within 4–8 weeks. Alternative dosing schedules of rituximab, such as 100 mg/week for 4 weeks, 1000mg on day 1 and day 15, or a single dose of 375 mg/m^2, have been explored in ITP patients showing similar short-term efficacy. With the clearance of rituximab from the body and the gradual recovery of B cells, most patients will relapse after 6 months.

Complications of ITP

The biggest and most worrisome complication associated with ITP is bleeding in the brain, according to the Mayo Clinic. This can be fatal. However, it is very rare.

Excessive bleeding during pregnancy can also be a problem for women with ITP. If you're pregnant and your platelet count is very low, your doctor may recommend treatment to prevent heavy bleeding.

ITP can also affect mental and emotional health, as well as overall quality of life. Symptoms like unexplained bruising may lead to embarrassment and social isolation. This may also be accompanied by depression and anxiety. Additionally, intense fatigue affects at least half of all adults with ITP.

Romiplostim

Romiplostim belongs to a class of drugs called TPO (thrombopoietin) peptide mimetics. These drugs help your body to make more platelets, which are cells that help your blood to clot.

Romiplostim works by mimicking the action of your own natural TPO, which is a hormone produced by your liver and kidneys that regulates how many platelets you produce. Romiplostim binds to and activates the same receptors that your own endogenous TPO uses to increase platelet production. It is a TPO receptor agonist. Romiplostim is a peptibody, which is a peptide fused to an antibody. It was the first fully engineered peptibody designed to stimulate platelet production and was approved by the US Food and Drug Administration (FDA) in 2008.

Clinical manifestations

The bleeding in ITP is mucocutaneous, manifesting as petechiae, purpura, easy bruising, epistaxis, gingival bleeding, and menorrhagia. ITP remains as a diagnosis of exclusion. In those patients with immune thrombocytopenia, typical clinical findings are missing after a detailed clinical history and physical exam.

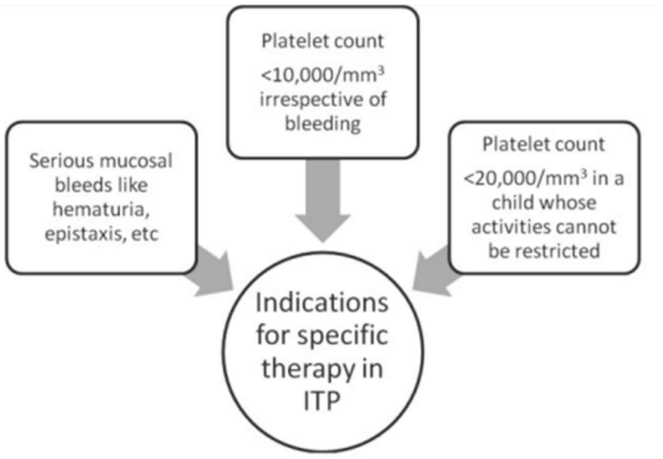


Fig 4: Managing ITP in children

Prognosis

The prognosis is good for acute ITP since most patients makes a spontaneous recovery. Patients with chronic ITP almost always require treatment, and relapse commonly occurs. A complete response to the first-line steroid can occur in about 20% of the patients, and about 60% have a partial response. Vincristine is used in adult patients that do not respond to splenectomy.

Complications

The most severe complication of ITP is hemorrhage, especially the rare complication of bleeding into the brain that may prove fatal.

Deterrence and patient education

The general practitioner can assess the bleeding and make recommendations about the management, and also a referral to a specialist (hematologist). The lack of definitive testing for ITP makes the diagnostic approach one of the eliminations of possible causes, ergo, a diagnosis of exclusion. Explaining the treatment of a 'presumptive' diagnosis to a patient may be a difficult task, but one made better if the patient improves with the modalities described here. Patient compliance is a priority.

Enhancing healthcare team outcomes

An interprofessional team should manage the patient with ITP. The clinicians and nursing staff may monitor subjects with a less severe disease if it does not involve important organ systems. The clinician should refer patients with complications to a hematologist, coordinating closely with the patient's clinician to maximize management and progress. The pharmacist should be involved in the coordination of drug therapy and monitoring for complications and interactions. All interprofessional team members must maintain accurate records of all interactions and interventions with the patient so all personnel involved in care have access to the same updated patient information. Open lines of communication are essential to ensure proper and timely care, particularly if any concerns arise, such as adverse effects or a deterioration in the patient's condition. An interprofessional team approach will result in the best outcomes.

CONCLUSION

ITP is a complex and heterogeneous disorder with uncertain etiology and ill-defined pathophysiology. Thrombocytopenia is the result of both increased platelet destruction and decreased platelet production, which is related to multiple abnormalities of the immune system in ITP. Diagnosis still relies on the exclusion of other thrombocytopenic diseases due to the lack of reliable biomarkers or gold-standard diagnostic tests. Although corticosteroids and IVIg remain the standard initial treatments for ITP, new explorations on the upfront use of agents such as TPO-RAs, MMF, and rituximab have depicted a landscape for future frontline therapies. Moreover, the emergence of novel agents targeting different pathogenetic mechanisms of ITP has deeply modified the second-line treatment modalities, which have gradually shifted away from immune suppression.

The disease can be perplexing because no confirmatory tests exist to ensure that physicians are not missing a more sinister diagnosis. The treatment options vary from doing nothing to using immunosuppressants and chemotherapy. The individualization of care based on the medical, social, and other supporting evidence is the difficult but ideal choice**.** Positive preliminary findings from ongoing clinical trials of TPO receptor agonists in ITP showing sustained increases in platelet counts in the majority of treated patients provide strong support for the role of TPO, megakaryocytopoiesis, and thrombopoiesis in ITP pathogenesis.

However, there are still unmet needs in ITP management, such as implementing precise individualized treatment, avoiding overtreatment, and handling multi-refractory cases. Therefore, the development of a stratification model capable of identifying patients who may truly benefit from treatment and guiding treatment selection is the priority research area. It would be better to incorporate the available clinical characteristics, immune profile, and environmental and genetic predispositions into the model, and validate it in future studies. Furthermore, precise shared decision-making tools should also be developed to optimize patient-specific treatment.

REFERENCES

1. Ponzetto A, Figura N, Fiorini G. Immune thrombocytopenic purpura and infections. Intern Emerg Med. 2018;13(7):1137. doi: 10.1007/s11739-018-1908-9, PMID 30030700.
2. Moulis G, Palmaro A, Montastruc JL, Godeau B, Lapeyre-Mestre M, Sailler L. Epidemiology of incident immune thrombocytopenia: a nationwide population-based study in France. Blood. 2014;124(22):3308-15. doi: 10.1182/blood-2014-05-578336, PMID 25305203.
3. Moulis G, Comont T, Adoue D. New insights into the epidemiology of immune thrombocytopenia in adult patients: impact for clinical practice. Rev Med Interne. 2021;42(1):11-5. doi: 10.1016/j.revmed.2020.05.018, PMID 32798089.
4. Weycker D, Hanau A, Hatfield M, Wu H, Sharma A, Bensink ME, et al. Primary immune thrombocytopenia in US clinical practice: incidence and healthcare burden in first 12 months following diagnosis. J Med Econ. 2020;23(2):184-92. doi: 10.1080/13696998.2019.1669329, PMID 31547724.
5. Matzdorff A, Wörmann B. Diagnosis and Therapy of Immune thrombocytopenia. Dtsch Med Wochenschr. 2018;143(15):1076-81. doi: 10.1055/a-0384-4703, PMID 30060276.
6. George JN. How I treat patients with thrombotic thrombocytopenic purpura: 2010. Blood. 2010;116(20):4060-9. doi: 10.1182/blood-2010-07-271445.
7. Cines DB, Blanchette VS. Immune thrombocytopenic purpura. N Engl J Med. 2002;346(13):995-1008. doi: 10.1056/NEJMra010501, PMID 11919310.
8. Abboud MR, Laver J, Xu F, Weksler B, Bussel JB. Serum levels of GM-CSF are elevated in patients with thrombocytopenia. Br J Haematol. 1996;92(2):486-8. doi: 10.1046/j.1365-2141.1996.d01-1464.x, PMID 8603021.
9. Zhou B, Zhao H, Yang RC, Han ZC. Multi- dysfunctional pathophysiology in ITP. Crit Rev Oncol Hematol. 2005;54(2):107-16. doi: 10.1016/j.critrevonc.2004.12.004, PMID 15843093.
10. Liu Y, Chen S, Sun Y, Lin Q, Liao X, Zhang J, et al. Clinical characteristics of immune thrombocytopenia associated with autoimmune disease: a retrospective study. Med (Baltim). 2016;95(50):e5565. doi: 10.1097/MD.0000000000005565, PMID 27977588.

11. Frederiksen H, Maegbaek ML, Nørgaard M. Twenty-year mortality of adult patients with primary immune thrombocytopenia: a Danish population-based cohort study. Br J Haematol. 2014;166(2):260-7. doi: 10.1111/bjh.12869, PMID 24690142.
12. Wang T, Zhao H, Ren H, Guo J, Xu M, Yang R, et al. Type 1 and type 2 T-cell profiles in idiopathic thrombocytopenic purpura. Haematologica. 2005;90(7):914-23. PMID 15996929.
13. Chang M, Nakagawa PA, Williams SA, Schwartz MR, Imfeld KL, Buzby JS, et al. Immune thrombocytopenic purpura (ITP) plasma and purified ITP monoclonal autoantibodies inhibit megakaryocytopoiesis in vitro. Blood. 2003;102(3):887-95. doi: 10.1182/blood-2002-05-1475, PMID 12676790.
14. Prasad VK, Kim IK, Farrington K, Bussel JB. TTP following ITP in an HIV-positive boy. J Pediatr Hematol Oncol. 1996;18(4):384-6. doi: 10.1097/00043426-199611000-00010, PMID 8888747.
15. Doobaree IU, Nandigam R, Bennett D, Newland A, Provan D. Thromboembolism in adults with primary immune thrombocytopenia: a systematic literature review and meta-analysis. Eur J Haematol. 2016;97(4):321-30. doi: 10.1111/ejh.12777, PMID 27199203.
16. Baron BW, Martin MS, Sucharetza BS, Jeon H-R, Baron JM. Four patients with both thrombotic thrombocytopenic purpura and autoimmune thrombocytopenic purpura: the concept of a mixed immune thrombocytopenia syndrome and indications for plasma exchange. J Clin Apher. 2001;16(4):179-85. doi: 10.1002/jca.1031, PMID 11835414.
17. Stein RS, Flexner JM. Idiopathic thrombocytopenic purpura during remission of thrombotic thrombocytopenic purpura. South Med J. 1984;77(12):1599-601. doi: 10.1097/00007611-198412000-00034, PMID 6542250.
18. Wang Y, Yu T, Dong Q, Liu S, Yu Y, Zhao HY, et al. Clonal hematopoiesis in primary immune thrombocytopenia. Blood Cancer J. 2022;12(3):40. doi: 10.1038/s41408-022-00641-5, PMID 35293382.
19. Rodeghiero F. ITP and thrombosis: an intriguing association. Blood Adv. 2017;1(24):2280. doi: 10.1182/bloodadvances.2017007989, PMID 29296876.
20. Lin HC, Huang J, Huang J, Zhang LJ, Yin XW, Yang JC et al. Concurrence of immune thrombocytopenic purpura and thrombotic thrombocytopenic purpura: a case report and review of the literature. J Med Case Rep. 2023;17(1):38. doi: 10.1186/s13256-023-03762-y, PMID 36750960.
21. Bussel JB, Cheng G, Saleh MN, Psaila B, Kovaleva L, Meddeb B, et al. Eltrombopag for the treatment of chronic idiopathic thrombocytopenic purpura. N Engl J Med. 2007;357(22):2237-47. doi: 10.1056/NEJMoa073275, PMID 18046028.
22. Visweshwar N, Ayala I, Jaglal M, Killeen R, Sokol L, Laber DA et al. Primary immune thrombocytopenia: a 'diagnosis of exclusion'? Blood Coagul Fibrinolysis. 2022;33(6):289-94. doi: 10.1097/MBC.0000000000001144, PMID 35867940.
23. Swan D, Newland A, Rodeghiero F, Thachil J. Thrombosis in immune thrombocytopenia: current status and future perspectives. Br J Haematol. 2021;194(5):822-34. doi: 10.1111/bjh.17390, PMID 33822358.
24. Torrez M, Chabot-Richards D, Babu D, Lockhart E, Foucar K. How I investigate acquired megaloblastic anemia. Int J Lab Hematol. 2022;44(2):236-47. doi: 10.1111/ijlh.13789, PMID 34981651.
25. Neunert C, Terrell DR, Arnold DM, Buchanan G, Cines DB, Cooper N, et al. American Society of Hematology 2019 guidelines for immune thrombocytopenia. Blood Adv. 2019;3(23):3829-66. doi: 10.1182/bloodadvances.2019000966, PMID 31794604.
26. Young NS. Aplastic anemia. N Engl J Med. 2018;379(17):1643-56. doi: 10.1056/NEJMra1413485, PMID 30354958.
27. Santoshi RK, Patel R, Patel NS, Bansro V, Chhabra G. A comprehensive review of thrombocytopenia with a spotlight on intensive care patients. Cureus. 2022;14(8):e27718. doi: 10.7759/cureus.27718, PMID 35949449.
28. Cooper N, Ghanima W. Immune thrombocytopenia. N Engl J Med. 2019;381(10):945-55. doi: 10.1056/NEJMcp1810479, PMID 31483965.
29. Vrbensky JR, Nazy I, Toltl LJ, Ross C, Ivetic N, Smith JW et al. Megakaryocyte apoptosis in immune thrombocytopenia. Platelets. 2018;29(7):729-32. doi: 10.1080/09537104.2018.1475637, PMID 29787328.
30. Kaushansky KK. Thrombopoietin: a tool for understanding thrombopoiesis. J Thromb Haemost. 2003;1(7):1587-92. doi: 10.1046/j.1538-7836.2003.00273.x, PMID 12871295.
31. Ingram M, Coopersmith A. Reticulated platelets following acute blood loss. Br J Haematol. 1969;17(3):225-9. doi: 10.1111/j.1365-2141.1969.tb01366.x, PMID 5806433.
32. Arnold DM, Dentali F, Crowther MA, Meyer RM, Cook RJ, Sigouin C, et al. Systematic review: efficacy and safety of rituximab for adults with idiopathic thrombocytopenic purpura. Ann Intern Med. 2007;146(1):25-33. doi: 10.7326/0003-4819-146-1-200701020-00006, PMID 17200219.
33. British Committee for Standards in Haematology General Haematology Task Force. Guidelines for the investigation and management of idiopathic thrombocytopenic purpura in adults, children and in pregnancy. Br J Haematol. 2003;120(4):574-96. doi: 10.1046/j.1365-2141.2003.04131.x, PMID 12588344.
34. Salama A, Mueller-Eckhardt C, Kiefel V. Effect of intravenous immunoglobulin in immune thrombocytopenia. Lancet. 1983;2(8343):193-5. doi: 10.1016/s0140-6736(83)90175-7, PMID 6135031.
35. Stasi R, Provan D. Management of immune thrombocytopenic purpura in adults. Mayo Clin Proc. 2004;79(4):504-22. doi: 10.4065/79.4.504, PMID 15065616.