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Review Article

Advances in the understanding and management of immune thrombocytopenia: a review of pathophysiology, risk factors, and treatment strategies

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ABSTRACT

An autoimmune disease known as immune thrombocytopenia (ITP) in which the immune system destroys platelets and the platelet count drops below 100,000/µl. The pathogenesis of ITP involves peripheral platelet destruction, impaired platelet production, and other mechanisms. Risk factors of ITP include environmental exposures, demographic factors, and genetic predispositions, all contributing to autoimmune responses. Diagnostic tests for ITP include complete blood count for low platelet counts, peripheral blood smear for platelet morphology, advanced autoantibody tests. Bone marrow examination for ruling out hematologic disorders, and spleen tissue analysis to understand platelet destruction and guide treatments. Treatment of ITP includes first-line therapies includes Corticosteroids, Intravenous immunoglobulin, anti-D immunoglobulin, second line therapies includes Rituximab, thrombopoietin receptor agonists, splenectomy and other therapies includes immuno-suppressants, and Fostamatinib. Some studies assessing response criteria in ITP patients. Recent advancement in ITP treatment involves spleen tyrosine kinase inhibitors, Bruton tyrosine kinase inhibitors, plasma cell-targeting agents, complement pathway, neuraminidase, and monoclonal antibodies. Also, in non-coding RNAs, CRISPR-associated protein 9 system, and Chimeric antigen receptor T-cell therapy. Recent research in ITP, animal models, includes in various species, mimic human ITP. This study concludes the understanding of ITP with various mechanisms and its advance therapies and treatment with ongoing latest research.

Keywords: Immune thrombocytopenia, Immunopathogenesis, ITP Risk factors, Treatments, Recent advancement

INTRODUCTION

Immune thrombocytopenia (ITP) is an autoimmune disorder resulting from T-cell dysfunction, lowers platelet count and increased bleeding leading to loss of immune tolerance.[1]

Types of ITP is classified as primary ITP in which "platelet count less than 100×109/l" with lack of cause and secondary ITP which is any form of ITP excluding primary ITP, including human immunodeficiency virus (HIV), hepatitis C virus (HCV), *Helicobacter pylori* (*H. pylori*) infection, systemic lupus erythematous (SLE), and lymphoproliferative disorder.[2]

In 2010, updated guidelines on ITP based International Working Group (IWG) criteria published, which defines ITP diagnosis categorized as acute, persistent, chronic, and refractory, corresponding respectively to <3 months, 3–12 months, >12 months, and failure post-splenectomy.[3]

The standard terminology and outcome criteria for ITP were established by the IWG at a conference in Vicenza, Italy, in October 2007. The final draft was approved during a brief conference at the "49th Annual Meeting of the

American Society of Haematology (ASH) in Atlanta on 08 December 2007".[4] The panel for this update includes 22 globally recognised experts in clinical and research aspects of ITP.[5]

The thrombosis normal mechanism starts activation and aggregation of platelets by endothelial damage, which is subsequently followed by the coagulation cascade forms a fibrin-stabilised thrombus. Eventually, plasmin uses fibrinolysis to break down the thrombus.[6]

Risk factors of ITP include environmental exposures (e.g., infections), demographic factors (young women, children, elderly), and genetic predispositions, all contributing to autoimmune responses.[4,7,8]

EPIDEMIOLOGY

Global prevalence of ITP around 10 to 23 cases/100,000 people.[9] In India, the prevalence of adult ITP is 9.5 cases/100,000.[10] In United Kingdom and France, the incidence rate is 23.9/100,000 men (older than 80 years) and 9.5/100,000 person-years (men older than 75 years) respectively.[11]

IMMUNOPATHOGENESIS OF ITP

The "immunopathogenesis" of ITP is a not a simple process it involves multiple process involving peripheral platelet destruction, impaired platelet production, and other mechanisms. This pathway is important to understand as it helps in discovering targeted therapies and improving patient outcomes.[12]

Peripheral platelet destruction

Autoantibodies target platelet membrane antigens, which cause platelet opsonization. Splenic macrophages of the mononuclear phagocytic system phagocytose antibody-opsonized platelets by identifying them via Fc receptors.[12] Macrophages present platelet antigens derived from phagocytosis, which activates the autoreactive CD4+ T-cells. The antigen presentation is critical in triggering the immunity response.[13] By the CD40L/CD40 pathway, activated CD4+ T-cells differentiate to become T-follicular helper T-cells (Tfh), which then activate the autoreactive B-cells. The activation of these B-cells is responsible for the generation of antibodies against platelets.[14] Plasma cells differentiated from the autoreactive B-cells generate anti-platelet antibodies. These antibodies are responsible for the increased destruction of platelets in the circulatory system (Figure 1).[15]

Impaired platelet production

Autoantibodies against glycoproteins such as GPIIb/IIIa and GPIb/IX on megakaryocytes stimulate antibody-dependent cellular cytotoxicity (ADCC) by macrophages it leads to impair platelet production in the bone marrow.[16] CD8+ T-cells, which are recruited to the spleen and bone marrow, which play a central role in platelet destruction and impaired production through cytotoxic actions. Then firstly, they target and then destroy platelets by recognizing antigens from MHC class I molecules, which can cause direct killing and apoptosis, reducing platelet counts in ITP. CD8+ T-cells mediate destruction through perforin and granzymes, causing platelet lysis and impairing platelet production by attacking megakaryocytes in the bone marrow.[14,17,18] Activated CD4+ T cells trigger anti-platelet antibody production, also causing increased platelet destruction.[19]

Thrombopoietin (TPO) is essential for platelet production because it stimulates megakaryocyte development under normal conditions, TPO level adjust to maintain normal platelet levels. Low levels of TPO in ITP despite reduced platelet counts.[20]

This occurs because TPO binds to autoantibody-coated platelets, reducing its circulation and impairing megakaryocyte stimulation, which exacerbates platelet deficiency (Figure 2).[18]

A reduced number or impaired function of regulatory T cells (Tregs) fails to counteract the autoimmune response, allowing the cycle of platelet destruction and impaired production to persist.[19]

Other mechanisms

Platelet desialylation leads to clearance by the "Ashwell-Morell receptor" in the liver, adding another layer of platelet loss in this autoimmune process.[21]

Increased platelet apoptosis, mediated by autoantibodies and cytotoxic T-cells, along with activation of the classical complement pathway, contributes to further platelet opsonization and destruction.[12]

RISK FACTORS ASSOCIATED WITH ITP

ITP has several risk factors, including environmental factors, genetic and demographic. Environmental risk factors for ITP including exposure to specific bacterial and viral infections, such as *H. pylori*, HCV, HIV, Epstein Barr virus (EBV), and autoimmune disorders, has been associated with the activation of autoimmune responses that contribute to ITP.[7]

Demographic risk factors for ITP include age and sex.[4] Genetic risk factors for ITP include specific gene polymorphisms. In literature, several gene variants associated with an increased risk of ITP.[8,22,23]

Environmental risk factors

Exposure to particular diseases, such as bacterial and viral infections, can trigger autoimmune reactions that lead to ITP, making it one of the environmental risk factors.

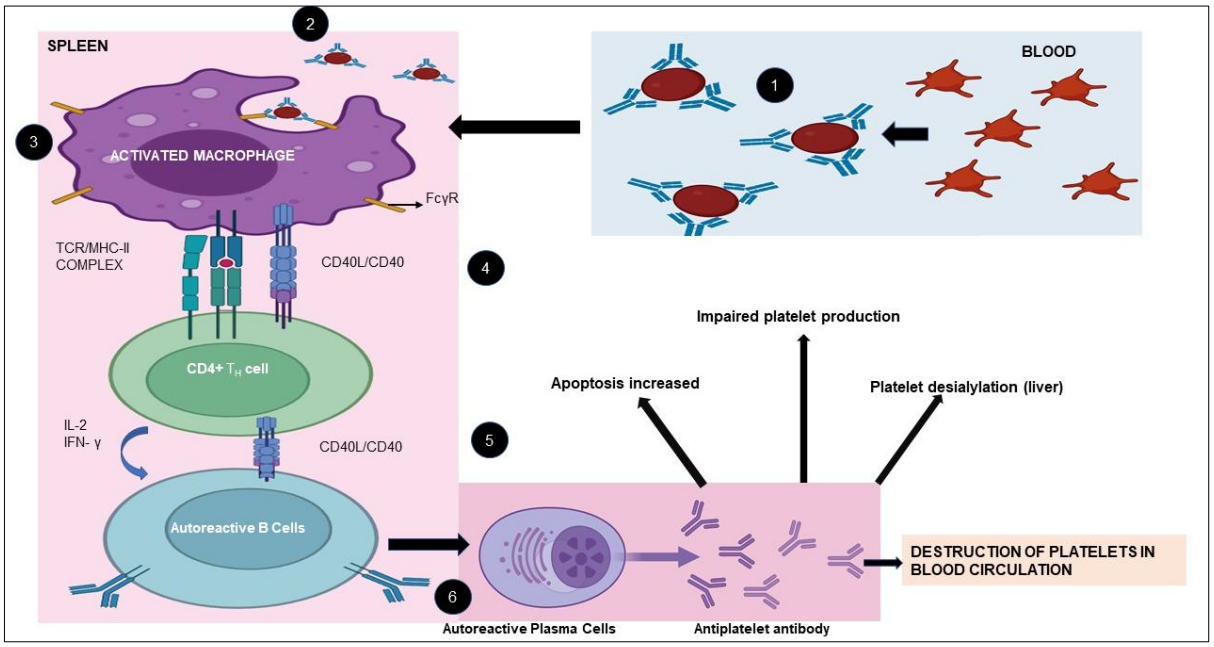

Figure 1: Pathogenesis of ITP- involve peripheral platelet destruction, 1) platelet opsonisation; 2) phagocytosis by splenic macrophage; 3) presentation of antigens; 4) activation of CD4+ T follicular helper cells; 5) T follicular helper cells stimulating autoreactive B cells; and 6) differentiation of B cells into plasma cells producing anti-platelet antibodies.[18]

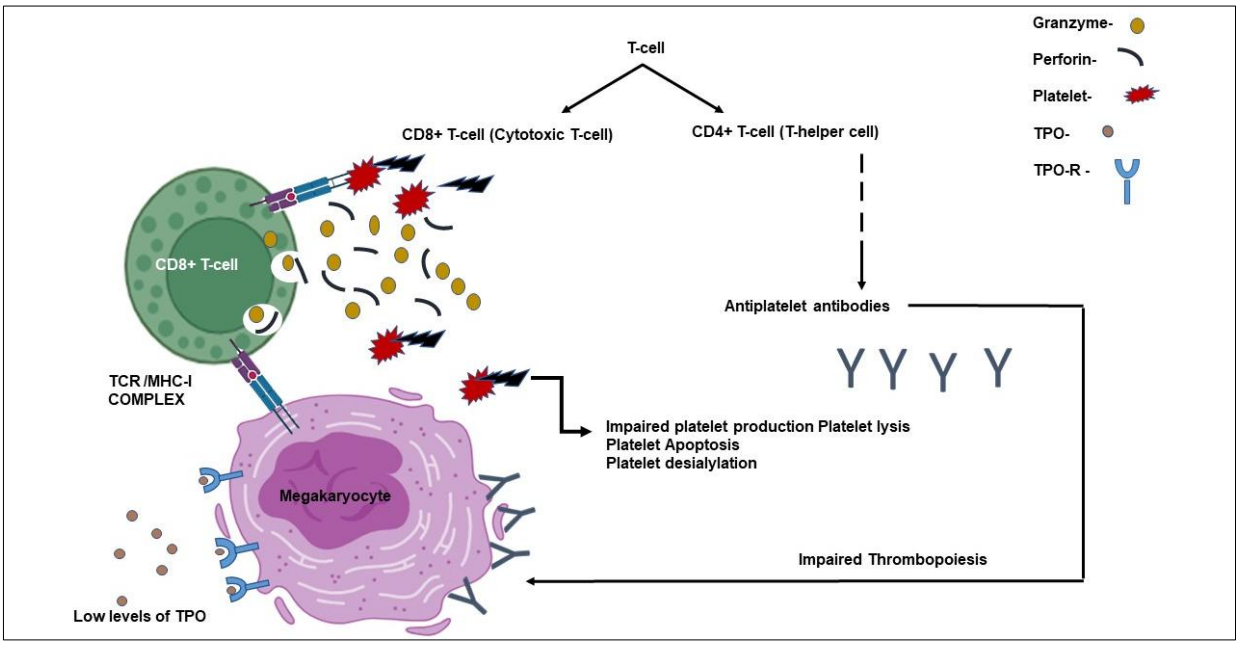

Figure 2: Pathogenesis of ITP before impaired platelet production in bone marrow.[12]

Note: TPO=Thrombopoietin, TPO-R = Thrombopoietin receptor.

***H. pylori* associated with ITP**

The risk factors for *H. pylori* infection can trigger ITP through immune system dysregulation, which results in low platelet counts. After eradication of the bacterium often resulting in increased platelet counts. The prevalence of *H. pylori* infection in ITP to be 28%, 40.9%, 22.1%, 81%, 59%, and 77.2% in India (Tamil Nadu), Egypt, Denmark, Pakistan, Iran, and Turkey, respectively.[24,25]

Pathogenesis of ITP in *H. pylori* infection due to *H. pylori* bacteria which normally possess many virulence factors that take a part in mechanism of *H. pylori*-ITP. It involves several processes includes molecular mimicry, antibody formation, and immune complex production, then resulting in the destruction of platelets and the

development of ITP.[26] In molecular mimicry *H. pylori* antigens, such as the CagA protein "cytotoxin-associated gene A", invade into the stomach mucosa and they can cross-react with platelet surface antigens like GP IIb/IIIa, Ib/IX, and Ia/IIa, then for inflammatory signalling they activate NF-κB (nuclear factor kappa B), which produces interleukin-8 (IL-8) causing gastritis.[21] Vacuolating cytotoxin A (VacA) is another virulence factor. When its gene is damaged, *H. pylori* infection induces pro-inflammatory cytokines, increasing the levels of "tumor necrosis factor-alpha" TNFα and IL-1β, and IL-6, causing autoimmune damage and inflammation, which then leads to ITP.[1] During antibody production, adhesin attachment helps the bacteria to evade the host immune response. This can cause the production of anti-platelet antibodies (e.g., anti-GPIIb/IIIa), which target platelets for destruction.[7] Immune complex formation consisting of *H. pylori* antigens and anti-platelet antibodies which activates the complement system and phagocytosis. This causes the destruction of platelets by immune complexes and phagocytic cells, reducing platelet lifespan and circulating platelet count, and ultimately leading to ITP.[26]

For diagnosing of *H. pylori* infection-ITP patients, non-invasive tests like the "urea breath test" and "stool antigen test". Invasive tests, such as "endoscopy with biopsy" prefers.[18]

Treatment strategies for *H. pylori* eradication therapy by using antibiotics such as "clarithromycin, amoxicillin, metronidazole and omeprazole".[24] Supportive care involves monitoring platelet counts and symptoms, managing bleeding with transfusions and hemostatic agents. For immunomodulatory therapy, corticosteroids and intravenous immunoglobulin (IVIG) therapy is used to increase platelet counts.[13]

HIV associated with ITP

HIV is higher risk group for thrombocytopenia because it promotes immune-mediated platelet destruction and reducing platelet production in the bone marrow. Several risk factors include low CD4+ counts, high viral loads, untreated HIV, opportunistic infections, and immune dysregulation.[27] In a recent meta-analysis, a worldwide prevalence of 17.9% among adults with HIV.[28] Thrombocytopenia affects 10% of HIV cases initially and correlates with low CD4+ T cell numbers and increased viral loads.[29]

In HIV patient ITP develops through antibody and T-cell-mediated platelet destruction. Patients who have not started antiretroviral therapy (ART) has more chances to occur Thrombocytopenia compared to those who started. It has higher morbidity, mortality, and faster disease progression.[26] Patients with low CD4+ counts <200 cells/µl have more chances to develop thrombocytopenia compared to those with high CD4+ counts ≥200 cells/µl.[29]

For diagnosis to exclude pseudo-thrombocytopenia and red cell fragments we use peripheral smear (P/s) and bone marrow biopsy for refractory cases or pre-splenectomy evaluation.[27] The introduction of highly active antiretroviral therapy (HAART) has significantly improved platelet counts and decrease HIV-ITP incidence rate.[28]

HCV associated with ITP

The risk factors for ITP in HCV patients involve autoantibodies targeting platelets, hypersplenism, virus-induced bone marrow suppression, and reduced TPO production, all contributing to the pathophysiology.[30]

In HCV patients, several risk factors for thrombocytopenia including lower platelet level, splenomegaly, and cirrhosis.[7] Thrombocytopenia is a frequent extrahepatic manifestation in viral hepatitis, including HCV, with a prevalence of 30.2/100,000, which is nearly double that of the HCV antibody-negative population.[30] ITP in HCV complicates diagnosis and treatment, affecting antiviral therapy initiation and outcomes. While direct-acting antivirals (DAAs) have advanced care, baseline thrombocytopenia may reduce sustained virologic response (SVR) rates, with growth factors offering potential support. Effective management of thrombocytopenia, particularly in advanced liver disease, is key to successful outcomes.[31]

The diagnosis of ITP in HCV patients is challenging due to the diverse array of pathologies or drug side effects that can cause thrombocytopenia.[20] Bone marrow biopsy is only advised for patients having ITP who have certain clinical manifestations or who are non-responsive to treatment.[16]

EBV associated with ITP

About 29.7% of adult patients with infectious mononucleosis experience thrombocytopenia.[32] Pathogenesis of ITP in EBV infection is not completely understood yet. While, a number of mechanisms have been suggested. According to one theory, autoantibodies are produced against platelet GPIIb-IIIa and Ib-IX, even though only 40% of people have autoantibodies.[7] ITP has a major effect on EBV infections and can cause life-threatening conditions and severe thrombocytopenia. Corticosteroids, IVIG, and platelet transfusions are available forms of treatment; refractory cases requiring specific methods.[32]

Autoimmune disorders associated with ITP

SLE associated with ITP

ITP occurs in 7-40% of SLE patients, with 8.35% diagnosed with ITP.[33] Platelet production impaired by immune dysregulation in SLE and elevated pro-inflammatory cytokines, While autoantibodies against platelet glycoproteins lead to increased platelet

destruction.[7] For diagnosis complete blood counts (CBC), Antinuclear antibodies (ANA) and autoimmune markers (anti-dsDNA, anti-Smith antibodies) can be done.[33] First-line treatment involves Corticosteroids, while others including azathioprine, mycophenolate mofetil, rituximab, and platelet transfusions for severe cases. Regular monitoring is essential in those case.[13]

Evans syndrome associated with ITP

About 2-5% of ITP patients develops Evans syndrome which is a rare autoimmune condition.[34] It involves autoantibodies targeting RBCs and platelets which leads to anemia, thrombocytopenia, and neutropenia. CBC, P/s, direct antiglobulin test (DAT), and bone marrow biopsy used for diagnosis.[35] First-line treatment involves Corticosteroids and IVIg with rituximab for refractory cases and for unresponsive patient's splenectomy can be done.[13]

APS- Antiphospholipid syndrome associated with ITP

APS linked to secondary ITP in about 20-50% of cases. ITP risk is increased by antiphospholipid antibodies (aPL), which activate and destroy platelets.[36] CBC, thrombotic events, and aPL testing (lupus anticoagulant, anti-cardiolipin, anti-beta2-glycoprotein I) used for diagnosis.[18]

For management it involves corticosteroids, anticoagulation therapy, IVIg, or for severe thrombocytopenia anti-D immunoglobulin can be used.[36]

CVID- Common variable immunodeficiency associated with ITP

CVID-ITP primarily occurs due to decreased platelet production rather than peripheral destruction, has prevalence is around 7-14 %.[37] Elevated "soluble interleukin-2 receptor" (sIL-2R) levels, CBC, decreased immunoglobulin levels (IgG, IgA, IgM), and lymphocyte subset analysis used in diagnosis.[38] Management involves immunoglobulin replacement therapy, for acute episodes corticosteroids used and rituximab as a second-line option, while patients who not respond to other therapies must go for splenectomy.[13]

Genetic risk factors

Hesham et al found that PTPN22 "Protein tyrosine phosphatase non-receptor 22 gene" which regulates immune responses by inhibiting B- and T-cell receptor signalling and inactivating autoreactive T lymphocytes, with the TT genotype increasing ITP risk.[22] Ghafar et al concluded that the rs2075876 AA genotype and A allele may increase the risk of ITP by influencing the AIRE (Autoimmune Regulator) gene, which is necessary for immune tolerance.[23]

According to Zhou et al, TNFAIP3, which encodes a protein that inhibits NF-κB signaling to regulate inflammation, may be linked to chronic ITP susceptibility through genetic variations that impair its regulatory function (Table 1).[39]

Table 1: Different genes associated with ITP.

Author, year, population	Gene	Findings	Conclusion
Hesham et al, 2021, Egyptian children[22]	PTPN22	PTPN22 1858C/T genotypes in patients showed 55% CC, 32.5% CT, and 12.5% TT, compared to 90%, 10%, and 0% in controls ($p<0.05$), with the T allele and TT genotype significantly increasing ITP risk	PTPN22 (1858 C>T) TT genotype significantly increases ITP risk in Egyptian children
Ghafar et al, 2023, Egyptian population[23]	AIRE	The study of two AIRE SNPs (rs2075876 G/A and rs760426 A/G) found that the "AIRE rs2075876" AA genotype and A allele were linked to increased ITP risk, with lower serum AIRE levels in patients, positively correlating with platelet counts. No association was found for rs760426	AIRE rs2075876 variants may contribute to ITP risk in the Egyptian population
Zhou et al, 2016, Chinese population[39]	TNFAIP3	The G allele and specific genotypes (TG rs2230926 and CG rs5029939) are linked to increased chronic ITP risk, potentially due to increased NF- κB activity and impaired dendritic cell function	TNFAIP3 genetic variations may contribute to chronic ITP development, but additional research is necessary to understand their precise role

Demographic parameters associated with ITP

ITP in children

The prevalence of pediatric ITP varies between 1.6 and 6 per 100,000 children and in Korea is 18.1 per 100,000 person-years.[4] Clinical symptoms of ITP in children often include easy bruising, petechiae, epistaxis, and there should no organomegaly and lymphadenopathy.[40] For acute cases no treatment required, but corticosteroids used as a primary therapy when intervention is needed. Treatment options for persistent

cases is TPO-RAs, rituximab, or splenectomy. Platelet levels must be regular monitored.[17] For diagnosis- CBC, clinical assessment for bleeding symptoms and additional tests (genotyping, immunophenotyping, and platelet function assays) for secondary causes. Bone marrow examination is not necessary unless atypical signs are present (lymphadenopathy or anaemia).[40]

ITP in adults

The incidence and prevalence of ITP in adults is around 3.3/100,000 per year and 9.5/100,000 individuals respectively, this increases with age, especially in those over 60 years old. It affects both sexes equally in older adults but more common in younger females.[41] Low platelet counts causes Easy bruising, petechiae, prolonged bleeding, frequent nosebleeds, heavy menstrual periods, and fatigue. Life-threatening internal bleeding can occur in severe cases.[42]

The diagnosis includes a P/s, a CBC to confirm isolated thrombocytopenia, and tests to detect underlying conditions such as *H. pylori*, HIV, HCV, and autoimmune disorders. Patients over 60 or those with unusual presentations are advised to have a bone marrow examination (BME).[20] First-line treatment includes "corticosteroids, IVIG, and anti-D immunoglobulin (anti-D Ig)", followed by second-line options such as "thrombopoietin receptor agonists (TPO-RAs), rituximab, fostamatinib, and splenectomy", with emerging therapies targeting specific pathways, such as Bruton tyrosine kinase (BTK) inhibitors and complement inhibitors, are under development to address ITP case.[20,41,42]

ITP in geriatrics

The incidence of ITP in 80 years old men and above is around 23.9 cases per 100,000 in UK, its particularly elevated in older adults.[11] When diagnosing ITP in older adults a CBC is used to confirm thrombocytopenia, additional tests are used to rule out secondary causes and considering the patient's overall health and comorbidities.[41]

For elder ITP patients different treatment strategies used due to higher risks of bleeding and thrombosis. Corticosteroids and IVIg are used as a First-line treatments, prolonged steroid use avoided to minimize side effects. Depend on the patient's health and comorbidities TPO-RAs or rituximab used as a second-line treatments.[43]

Gender

According to a study, 77.2% of ITP cases are in females, shows a significant difference in gender. Particularly ITP in adults, more common in women than men.[44]

ITP during pregnancy

One to two cases of ITP occur for every 1,000 to 10,000 pregnancies.[45,46] Maternal bleeding can occur during delivery and potential neonatal thrombocytopenia is also a complications of ITP which can occur during pregnancy. These complications can cause severe postpartum haemorrhage in mother and bleeding risks for the new-born, including intracranial haemorrhage.[46] Treatment of ITP during pregnancy involves corticosteroids and IVIG to maintain platelet counts and "TPO-RAs and rituximab" used as second-line options. Regular monitoring of platelet levels is crucial especially near delivery to reduce bleeding risks. Prolonged corticosteroid use needs careful management to avoid side effects.[45]

ONGOING RESEARCH STUDIES

Animal model of ITP

In animal models when we injected with anti-platelet antiserum or monoclonal antibody it mimic human ITP and causes thrombocytopenia within 24 hours. Various animal models like mice, rats, rabbits, and dogs have been used to study autoimmune platelet destruction which mimics the autoimmune platelet destruction observed in human ITP.[47] Gonzalez et al examined "17CO2-based molecules" in FcγR-humanized mice, using 17CO2-albumin and 17CO2-IgG2a, with human albumin as a control. Their findings show potential benefits for ITP treatment.[48] Other studies also have investigated with different approaches, such as monoclonal rat anti-mouse CD41 antibodies and involvement of CD8+ T- cell in platelet destruction.[49,50] Using a murine IgG2a monoclonal antibody, a canine model also showed a significant reduction in platelets without causing systemic inflammation.[47]

DIAGNOSTIC TESTS FOR ITP

Blood samples

Used to analyse biomarkers, autoantibodies, and platelet counts, which help to diagnose ITP.[21] CBC is vital in diagnosing ITP, as it typically shows a decrease in platelet count ($<100\times10^9$/l) while other blood cell counts remain normal, aiding in the confirmation of the condition.[51] Peripheral blood smear (P/s) performed with CBC, which can provide additional insights of morphology of the platelets and other blood cells. In ITP typically shows normal platelet morphology but may also reveal larger platelets (megathrombocytes) and small platelet fragments (micro-particles), which indicates low platelet counts.[51,52] Pseudo-thrombocytopenia caused by platelet clumping which must be excluded to evaluate ITP.[42]

There are some recent advancements in autoantibody testing for diagnosing ITP focus on improving sensitivity and specificity. Platelet autoantibody testing detects specific autoantibodies against platelet glycoproteins are-

monoclonal antibody immobilization of platelet antigens (MAIPA) and enzyme-linked immunosorbent assay (ELISA) are used for ITP diagnosis.[43]

Flow cytometry used for ITP diagnosis. It quantifies platelet-associated antibodies, and detects elevated levels of platelet-associated immunoglobulins (PAIg), with high sensitivity and specificity.[44]

Bone marrow examination

BME is used in patients with ITP to rule out other hematologic disorders, but is generally recommended against routine use due to potential diagnostic error.[21] BME assesses platelet production and megakaryocyte abnormalities.[51]

Spleen tissue samples

Spleen tissue samples are analyzed in ITP to understand platelet destruction mechanisms, differentiate from other conditions, and guide treatment decisions post-splenectomy.[21]

TREATMENT OF ITP

Treatment of ITP depends on various factors such as platelet count, bleeding symptoms, and patient age. Corticosteroids, IVIG or anti-D Ig used as a first-line treatments to improve platelets. Rituximab or TPO-RAs used as second-line options only when the ineffective first line treatment or if the condition relapses. Splenectomy or other immunosuppressive therapies might be recommended in refractory cases (Tables 2 and 3).

RECENT ADVANCEMENT IN ITP

Recent advancements in understanding the complete pathogenesis of ITP is way for innovative treatment approaches. SYK inhibitors, BTK inhibitors, and plasma cell-targeting agents these specific targets take part in developing new therapies. Additionally, treatments that block the classical complement pathway, inhibit the neonatal Fc receptor, and stop platelet desialylation have the potential to enhance ITP management. This review provides an overview of these current strategies and emerging therapies in the field of ITP (Table 4).[41]

Table 2: Overview of ITP treatment.

Therapy type, treatment options and its uses	Mechanism of action	Response/ effectiveness	Recommended dose
First-line therapies			
Corticosteroids (e.g., Prednisone, Dexamethasone), Initial treatment for increasing platelets[41]	Suppresses immune response, reduces autoantibody production	70-80% respond; limited by long-term side effects	Prednisone-1 mg/kg/day (max 80 mg) for 2-3 weeks, Dexamethasone-40 mg/day for 4 days, repeat upto 3 times
IVIg rapid platelet count increase in emergencies[41,52]	Blocks Fc receptors on macrophages, reducing platelet destruction	Short-term effect; temporary solution	1-2 days- 0.8-1 g/kg or for 4-5 days- 0.4-0.5 g/kg
Anti-D Ig used in Rh-positive, spleen-intact patients[13]	Induces destruction of Rh-positive red blood cells to spare platelets	Short-term measure	50-75 µg/kg administered intravenously as a single dose
Second-line therapies			
Rituximab for corticosteroid-refractory patients[52]	Targets CD20 on B cells, lowering autoantibody production	40-60% response; relapses are common	375 mg/m^2/week intravenously for 4 weeks
TPO-RAs (Eltrombopag, Romiplostim, Avatrombopag) Used in cITP or after first-line treatment failure[21,41]	Mimics thrombopoietin, stimulating platelet production	Effective in 70-80% of cases; long-term therapy	Eltrombopag: 50 mg/day (upto 75 mg/day), Romiplostim: 1 µg/kg/week subcutaneously (upto 10 µg/kg/week); Avatrombopag: 20 mg/day (upto 40 mg/day)
Splenectomy for non-responsive or cITP patients[13,41]	Reduces platelet destruction by removing the spleen	60-70% achieve long-term remission, but with surgical risks	–
Other therapies			
Immuno-suppressants (Azathioprine, Mycophenolate Mofetil, Cyclosporine) for refractory cases[12,2]	Suppresses overall immune function	Effective but with significant side effects	Azathioprine: 1-2 mg/kg/day (max 150 mg/day), Cyclosporin A: 5 mg/kg/day initially, then 2.5-3 mg/kg/day, Cyclophosphamide: 1-2

Continued.

Therapy type, treatment options and its uses	Mechanism of action	Response/ effectiveness	Recommended dose
			mg/kg/day orally or 0.3-1 g/m² IV every 2-4 weeks
Fostamatinib cITP after failure of other treatments[42]	Inhibits spleen tyrosine kinase (SYK) to decrease platelet destruction	18-44% response rate	100 mg twice daily, up to 150 mg if needed

Table 3: Comprehensive list of studies assessing response criteria in ITP patients.

Author, year, and population	Treatment	Findings	Conclusion
Beyene et al, 2024, 214 Ethiopian ITP patients, 75.5% female[45]	Standard treatment	83.2% adherence; complete response (CR): 65% at 3 months, 76.2% at 12 months	High adherence and CR at 12 months in Ethiopian patients
Bussel et al, 2014, 67 ITP patients treated in the USA[46]	Rituximab + dexamethasone	12 patients (18%) partial response (PR) after 8 weeks; 50 out of 67 patients (75%) best response; median 64 days to PR	combination therapy is effective but requires relapse monitoring
Khera et al, 2020, 44 North Indian paediatric patients with refractory ITP and 29 analysed[53]	Dapsone therapy	Children with refractory ITP—unresponsive to splenectomy, rituximab, or eltrombopag—were treated with dapsone, resulting in a 72% overall response rate, with 24% CR and 48% PR	Dapsone is an effective and affordable treatment for paediatric chronic refractory ITP in resource-poor settings, offering SR suitable as both a bridge therapy and a long-term alternative to costlier options
Rast et al, 2024, 46 adult ITP patients (27 newly diagnosed, 19 relapsed) from the Eastern Austria[54]	Standard treatments (corticosteroids, IVIG, TPO-RAs, rituximab)	First-line prednisolone showed an 82.6% response in 10 days (newly diagnosed: 8 days; relapsed: 14 days); 50% of patients (40.7% newly diagnosed, 63.2% relapsed) required second-line TPO-RAs, achieving a 73.7% response in 15 days	Corticosteroids are effective for most ITP patients; though long-term remission is achieved in only half. TPO-RAs are effective second-line treatments, enabling faster therapy transitions and reducing splenectomy need, as per updated guidelines

Table 4: Recent advances in targeted therapeutics for ITP.

Target therapeutics	Drug examples	Mechanism of action	Target cell
BTK inhibitors[9]	Rilzabrutinib	BTK is a key target in treating ITP because of its role in B-cell development, antibody production, and the regulation of immune cell responses. Inhibiting BTK can help reduce autoimmune activity by lowering antibody production and reducing inflammation. Rilzabrutinib, an oral BTK inhibitor, can impact multiple immune processes, leading to rapid and lasting anti-inflammatory effects.	Primarily target B cells, they also impact macrophages
SYK inhibitors[42]	Fostamatinib	Syk inhibitors like fostamatinib, treat ITP by blocking the Syk enzyme, which is involved in the immune system's destruction of platelets. In ITP, the immune system targets platelets for removal via Fcγ receptor signalling on immune cells. Syk inhibitors disrupt this signalling, preventing the immune cells from destroying platelets, thereby increasing platelet counts and reducing the risk of bleeding.	Macrophage
Proteasome inhibitors[41]	Bortezomib, KZR-616	Plasma cell-targeting therapies decrease antiplatelet antibodies by reducing both short- and long-lived plasma cells. Proteasome inhibitors disrupt proteasome function, leading to the accumulation of pro-apoptotic factors that promote plasma cell death and lower antibody production.	Plasma cell

Continued.

Target therapeutics	Drug examples	Mechanism of action	Target cell
FcRn (anti-neonatal Fc receptor) inhibitors[13]	Rozanolixizumab	Humanised monoclonal antibody rozanolixizumab blocks IgG interaction by attaching to the IgG-binding region of FcRn. This interference reduces IgG recycling and promotes its degradation in lysosomes, leading to decreased IgG levels in the body.	Antiplatelet antibodies
Complement pathway inhibitors[41]	Sutimlimab	Inhibits the classical complement pathway to prevent platelet destruction	Classical complement pathway
Neuraminidase inhibitors (NI)[12]	Oseltamivir	Inhibition of platelet desialylation. Oseltamivir, a NI, can lead to an unexpected rise in platelet counts in ITP patients. This happens because NIs reduce sialic acid on the platelet surface, making them less likely to be cleared by the reticuloendothelial system	Platelet
Monoclonal antibodies[55]	Rituximab, combination of belimumab with rituximab	Rituximab, a monoclonal antibody targeting CD-20 on B-cells, depletes B-cells in ITP through mechanisms like ADCC, complement-mediated lysis, and apoptosis. This reduces the production of antiplatelet antibodies, improving platelet levels	B-cells

Non-coding RNA

Hematological disorders like ITP, linked to the dysregulation of non-coding RNAs (ncRNAs). Focusing on specific miRNAs (microRNAs) or lncRNAs (long non-coding RNAs) which offers the possibility of restoring proper megakaryocyte function and increasing platelet production.[56] Recent studies have shown that microRNAs-155 “miR-155” targets SOCS1 “suppressor of cytokine signalling-1” to initiates ITP, while lower expression of “miR-130A” also contributes by targeting TGF-β1 “transforming growth factor beta 1”and IL-18.[56,57] On the other hand, “miR-155-5p” can also prevents ITP by upregulating SOCS1 and promoting PD-1/PDL1-mediated macrophage M2 polarization.[58] Similarly, "miR-106b-5p" causes immunological dysregulation in Treg/Th17 cells via the nuclear receptor subfamily 4 group A member 3/forkhead box protein 3 gene "NR4A3/Foxp3" pathway, while "miR-557" prevents megakaryocyte differentiation.[56]

Similarly, long non-coding RNAs “lncRNAs” also mediate immunosuppressive response of Tregs at the post-transcriptional stage. Among lncRNAs, TMEVPG1 “Theiler's murine encephalitis virus possible gene1” stimulates IFN-γ “interferon gamma” transcription to slow ITP progression, and MEG3 “maternally expressed gene 3” induces immune imbalance by inhibiting miR-125a-5p, affecting Treg/Th17 cells.[59]

CRISPR-associated protein 9 (Cas9) system

The CRISPR-Cas9 is a powerful tool for gene editing. Gene editing can also rectify genetic alterations associated with ITP or disrupt genes essential for the maturation and function of autoreactive immune cells.[16]

Chimeric antigen receptor T-cell (CAR T-cell) therapy

CAR T-cell therapy is a potential treatment for ITP, which was traditionally utilized in cancer treatment and now shows a significant advancement in ITP.[55] In this therapy, patient's T-cells alter to express a CAR, this treatment enables the cells to recognize and attach to particular targets autoimmune response that drives ITP. Once they activated these CAR T-cells may reduce the aberrant destruction of platelets by releasing cytokines that triggers the immune response.[16] Zhou et al developed GPIbα CAAR T cells “chimeric autoantibody receptor T cells” that selectively eliminate autoreactive B cells in ITP while preserving healthy B cells, showing efficacy in reducing autoantibody levels and thus presenting a potential new treatment option for refractory and relapsed ITP patients.[60] This targeted approach offers a new source of hope for patients with severe, treatment-resistant ITP, presenting a novel way to regulate immune activity and improve outcomes.

CONCLUSION

This study understands ITP through various mechanisms, highlighting the importance of its pathophysiology and heterogeneity in different risk factors. Current research efforts are directed toward uncovering these complexities and developing innovative therapeutic strategies. Future advancements are expected to yield more effective therapies and treatments for ITP.

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REFERENCES

1. Schoenaker JM, Nelson VS, Henderickx JGE, Terveer EM, Jansen AJG, Porcelijn L, et al. The intestinal flora: The key to unraveling heterogeneity in immune thrombocytopenia? Blood Rev. 2025;69:101252.
2. Provan D, Stasi R, Newland AC, Blanchette VS, Bolton-Maggs P, Bussel JB, et al. International consensus report on the investigation and management of primary immune thrombocytopenia. Blood. 2010;115(2):168-86.

3. Grace RF, Long M, Kalish LA, Neufeld EJ. Applicability of 2009 International Consensus Terminology and Criteria for Immune Thrombocytopenia to a Clinical Pediatric Population. Pediatr Blood Cancer. 2012;58(2):216-20.
4. Rosu VE, Roșu ST, Ivanov AV, Starcea IM, Streanga V, Miron IC, et al. Predictor Factors for Chronicity in Immune Thrombocytopenic Purpura in Children. Children (Basel). 2023;10(6):911.
5. Rodeghiero F, Stasi R, Gernsheimer T, Michel M, Provan D, Arnold DM, et al. Standardization of terminology, definitions and outcome criteria in immune thrombocytopenic purpura of adults and children: report from an international working group. Blood. 2009;113(11):2386-93.
6. Litvinov RI, Weisel JW. Blood clot contraction: Mechanisms, pathophysiology, and disease. Res Pract Thromb Haemost. 2023;7(1):100023.
7. Cines DB, Bussel JB, Liebman HA, Luning Prak ET. The ITP syndrome: pathogenic and clinical diversity. Blood. 2009;113(26):6511-21.
8. Georgi JA, Middeke JM, Bornhäuser M, Matzdorff A, Trautmann-Grill K. Deciphering the genetic basis of immune thrombocytopenia: current evidence for genetic predisposition in adult ITP. Blood Adv. 2023;7(14):3710-24.
9. Kuter DJ, Mayer J, Efraim M, Bogdanov LH, Baker R, Kaplan Z, et al. Long-term treatment with rilzabrutinib in patients with immune thrombocytopenia. Blood Adv. 2024;8(7):1715-24.
10. Kalal S, Suresh K. Immune Thrombocytopenic Purpura - A Recurrent Case in a Young Lady. Acta Sci Womens Health. 2021;3(6):135-8.
11. Crickx E, Mahévas M, Michel M, Godeau B. Older Adults and Immune Thrombocytopenia: Considerations for the Clinician. Clin Interv Aging. 2023;18:115-30.
12. Audia S, Mahévas M, Nivet M, Ouandji S, Ciudad M, Bonnotte B. Immune Thrombocytopenia: Recent Advances in Pathogenesis and Treatments. Hemasphere. 2021;5(6):e574.
13. Mititelu A, Onisâi MC, Roșca A, Vlădăreanu AM. Current Understanding of Immune Thrombocytopenia: A Review of Pathogenesis and Treatment Options. Int J Mol Sci. 2024;25(4):2163.
14. Audia S, Mahévas M, Samson M, Godeau B, Bonnotte B. Pathogenesis of immune thrombocytopenia. Autoimmun Rev. 2017;16(6):620-32.
15. Lv Y, Shi H, Liu H, Zhou L. Current therapeutic strategies and perspectives in refractory ITP: What have we learned recently? Front Immunol. 2022;13:953716.
16. Madkhali MA. Recent advances in the management of immune thrombocytopenic purpura (ITP): A comprehensive review. Medicine (Baltimore). 2024;103(3):e36936.
17. Kistanguri G, McCrae KR. Immune Thrombocytopenia. Hematol Oncol Clin North Am. 2013;27(3):495-520.
18. Martínez-Carballeira D, Bernardo Á, Caro A, Soto I, Gutiérrez L. Pathophysiology, Clinical Manifestations and Diagnosis of Immune Thrombocytopenia: Contextualization from a Historical Perspective. Hematol Rep. 2024;16(2):204-19.
19. Provan D, Semple JW. Recent advances in the mechanisms and treatment of immune thrombocytopenia. EBioMedicine. 2022;76:103820.
20. González-López TJ, Newland A, Provan D. Current Concepts in the Diagnosis and Management of Adult Primary Immune Thrombocytopenia: Our Personal View. Medicina (Kaunas). 2023;59(4):815.
21. Matzdorff A, Alesci SR, Gebhart J, Holzhauer S, Hütter-Krönke ML, Kühne T, et al. Expert Report on Immune Thrombocytopenia: Current Diagnostics and Treatment – Recommendations from an Expert Group from Austria, Germany, and Switzerland. Oncol Res Treat. 2023;46(2):5-44.
22. Hesham M, Hassan T, Fawzy A, Mohamed N, Alhejny E, Fathy M, et al. PTPN22 gene polymorphism as a genetic risk factor for primary immune thrombocytopenia in Egyptian children. Expert Rev Hematol. 2021;14(9):877-81.
23. Abdel Ghafar MT, Elshora OA, Allam AA, Mashaal RG, Hamous SAA, Abd El-Khalik SR, et al. Autoimmune Regulator Gene Polymorphisms and the Risk of Primary Immune Thrombocytopenic Purpura: A Case-Control Study. Int J Mol Sci. 2023;24(5):5007.
24. Pezeshki SMS, Saki N, Ghandali MV, Ekrami A, Avarvand AY. Effect of Helicobacter Pylori eradication on patients with ITP: a meta-analysis of studies conducted in the Middle East. Blood Res. 2021;56(1):38-43.
25. Kumar SM, Natarajan M, Vasudevan P, Prakash V, Kalyani VD. Prevalence of Helicobacter pylori infection in adult immune thrombocytopenia patients. Asian J Med Sci. 2023;14(10):128-32.
26. Takeuchi H, Okamoto A. Helicobacter pylori Infection and Chronic Immune Thrombocytopenia. J Clin Med. 2022;11(16):4822.
27. Lv X, Li P, Yue P, Tang P, Zhou F. Risk factors and prognosis of thrombocytopenia in people living with HIV/AIDS. Ther Adv Hematol. 2023;14:20406207231170513.
28. Getawa S, Aynalem M, Bayleyegn B, Adane T. The global prevalence of thrombocytopenia among HIV-infected adults: A systematic review and meta-analysis. Int J Infect Dis. 2021;105:495-504.
29. Talargia F, Getacher L. Thrombocytopenia and Associated Factors Among HIV Infected Patients in Pre- and Post-Anti-Retroviral Therapy, North East Ethiopia. J Blood Med. 2021;12:741-8.
30. Xu Y, Chen Y, Zhang L. Review: Advances in the Pathogenesis and Treatment of Immune Thrombocytopenia Associated with Viral Hepatitis. Glob Med Genet. 2023;10(3):229-33.
31. Dahal S, Upadhyay S, Banjade R, Dhakal P, Khanal N, Bhatt VR. Thrombocytopenia in Patients with

Chronic Hepatitis C Virus Infection. Mediterr J Hematol Infect Dis. 2017;9(1):e2017019.
32. Páez-Guillán EM, Campos-Franco J, Alende R, Gonzalez-Quintela A. Hematological Abnormalities Beyond Lymphocytosis During Infectious Mononucleosis: Epstein-Barr Virus-Induced Thrombocytopenia. Mediterr J Hematol Infect Dis. 2023;15(1):e2023023.
33. Cornudella Lema J, Sánchez-González B, Carrión-Barberà I, Vázquez Montes de Oca S, García Pallarols F, Salman-Monte TC. Immune thrombocytopenia in systemic lupus erythematosus: Prevalence, risk factors, and a novel predictive model for risk assessment. Med Clin (Barc). 2024;162(10):461-9.
34. Michel M. Adult Evans' Syndrome. Hematol Oncol Clin North Am. 2022;36(2):381-92.
35. Fattizzo B, Carrai V, Crugnola M, Baldacci E, Bellini M, Bosi C, et al. Evans syndrome: Disease awareness and clinical management in a nation-wide ITP-NET survey. Eur J Haematol. 2024;113(4):472-6.
36. Tomasello R, Giordano G, Romano F, Vaccarino F, Siragusa S, Lucchesi A, et al. Immune Thrombocytopenia in Antiphospholipid Syndrome: Is It Primary or Secondary? Biomedicines. 2021;9(9):1170.
37. Mormile I, Punziano A, Riolo CA, Granata F, Williams M, de Paulis A, et al. Common Variable Immunodeficiency and Autoimmune Diseases: A Retrospective Study of 95 Adult Patients in a Single Tertiary Care Center. Front Immunol. 2021;12:652487.
38. Somasundaram N, Meyer O, Scheibenbogen C, Hanitsch LG, Stittrich A, Kölsch U, et al. Clinical and immunological characterisation of patients with common variable immunodeficiency related immune thrombocytopenia. Clin Exp Med. 2023;23(8):5423-32.
39. Zhou H, Yang J, Liu L, Zhang D, Zhou K, Li H, et al. The polymorphisms of tumor necrosis factor-induced protein 3 gene may contribute to the susceptibility of chronic primary immune thrombocytopenia in Chinese population. Platelets. 2016;27(1):26-31.
40. Faki Osman ME. Childhood immune thrombocytopenia: Clinical presentation and management. Sudan J Paediatr. 2012;12(1):27-39.
41. Kim DS. Recent advances in treatments of adult immune thrombocytopenia. Blood Res. 2022;57(1):112-9.
42. 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.
43. Kelton JG, Vrbensky JR, Arnold DM. How do we diagnose immune thrombocytopenia in 2018? Hematology Am Soc Hematol Educ Program. 2018;2018(1):561-7.
44. Tomer A, Koziol J, Mcmillan R. Autoimmune thrombocytopenia: flow cytometric determination of platelet-associated autoantibodies against platelet-specific receptors. J Thromb Haemost. 2005;3(1):74-8.
45. Beyene DA, Sisay EA, Fentie AM, Gebremedhin A. Treatment outcomes and adherence to treatment in patients with immune thrombocytopenia in two Ethiopian teaching hospitals: a retrospective cohort study. Sci Rep. 2024;14(1):11917.
46. Bussel JB, Lee CS, Seery C, Imahiyerobo AA, Thompson MV, Catellier D, et al. Rituximab and three dexamethasone cycles provide responses similar to splenectomy in women and those with immune thrombocytopenia of less than two years duration. Haematologica. 2014;99(7):1264-71.
47. Semple JW. Animal models of immune thrombocytopenia (ITP). Ann Hematol. 2010;89(1):37-44.
48. Gil Gonzalez L, Won KD, Tawhidi Z, Cummins E, Cruz-Leal Y, Tundidor Cabado Y, et al. Human Fc gamma receptor IIIA blockade inhibits platelet destruction in a humanized murine model of ITP. Blood Adv. 2024;8(8):1869-79.
49. Neschadim A, Branch DR. Mouse Models for Immune-Mediated Platelet Destruction or Immune Thrombocytopenia (ITP). Curr Protoc Immunol. 2016;113(1):15.
50. Chow L, Aslam R, Speck ER, Kim M, Cridland N, Webster ML, et al. A murine model of severe immune thrombocytopenia is induced by antibody- and CD8+ T cell–mediated responses that are differentially sensitive to therapy. Blood. 2010;115(6):1247-53.
51. Parmar RA, Patel KA. Immune Thrombocytopenic Purpura (ITP): A Comprehensive Review. GAIMS J Med Sci. 2024;4(1):103-7.
52. Russo G, Parodi E, Farruggia P, Notarangelo LD, Perrotta S, Casale M, et al. Recommendations for the management of acute immune thrombocytopenia in children. A Consensus Conference from the Italian Association of Pediatric Hematology and Oncology. Blood Transfus. 2024;22(3):253-65.
53. Khera S, Pramanik SK, Yanamandra U, Mishra K, Kapoor R, Das S. Dapsone: An Old but Effective Therapy in Pediatric Refractory Immune Thrombocytopenia. Indian J Hematol Blood Transfus. 2020;36(4):690-4.
54. Rast J, Schramm T, Mehic D, Fillitz M, Drexel T, Neusiedler-Nicolas V, et al. Management of Adult Patients with Newly Diagnosed or Relapsed Primary Immune Thrombocytopenia in Eastern Austria. Hämostaseologie: 2024; 5.
55. Cheekati M, Murakhovskaya I. Anti-B-Cell-Activating Factor (BAFF) Therapy: A Novel Addition to Autoimmune Disease Management and Potential for Immunomodulatory Therapy in Warm Autoimmune Hemolytic Anemia. Biomedicines. 2024;12(7):1597.
56. Li W, Lv Y, Sun Y. Roles of non-coding RNA in megakaryocytopoiesis and thrombopoiesis: new target therapies in ITP. Platelets. 2023;34(1):2157382.

57. Qian BH, Ye X, Zhang L, Sun Y, Zhang JR, Gu ML, et al. Increased miR-155 Expression in Peripheral Blood Mononuclear Cells of Primary Immune Thrombocytopenia Patients Was Correlated with Serum Cytokine Profiles. Acta Haematol. 2014;133(3):257-63.
58. Chang Y, Chen X, Tian Y, Gao X, Liu Z, Dong X, et al. Downregulation of microRNA-155-5p prevents immune thrombocytopenia by promoting macrophage M2 polarization via the SOCS1-dependent PD1/PDL1 pathway. Life Sci. 2020;257:118057.
59. Li H, Hao Y, Zhang D, Fu R, Liu W, Zhang X, et al. Aberrant expression of long noncoding RNA TMEVPG1 in patients with primary immune thrombo -cytopenia. Autoimmunity. 2016;49(7):496-502.
60. Zhou J, Xu Y, Shu J, Jiang H, Huang L, Xu M, et al. GPIbα CAAR-T cells function like a Trojan horse to eliminate autoreactive B cells to treat immune thrombocytopenia. Haematological. 2024;109(7):2256-70.

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