Immune Thrombocytopenia (ITP) In Emergency Medicine


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Abstract: Immune Thrombocytopenia (ITP) is an autoimmune disorder characterised by a low platelet count less than 100 × 10^9/L, purpura, and hemorrhagic episodes induced by antiplatelet autoantibodies without anaemia or leukopenia. Immune thrombocytopenia (ITP) occurs in 2 to 4/10000 adults. A wide range of signs and symptoms, from modest mucocutaneous petechiae to severe, life-threatening organ haemorrhage, are seen in ITP patients. They may present to the emergency department (ED) with life-threatening bleeding as a result of their thrombocytopenia. ITP has two distinct clinical syndromes, manifesting as an acute condition in children and a chronic condition in adults. IgG autoantibodies make circulating platelets more sensitive. It causes these cells to be removed more quickly by antigen-presenting cells (macrophages) of the spleen, and occasionally the liver or other components of the monocyte-macrophage system. Current evidence supports alternatives to splenectomy for second-line management of patients with persistently low platelet counts and bleeding. By increasing platelet production, bone marrow compensates for platelet breakdown. Immune Thrombocytopenia most commonly arises within a few weeks after a viral infection in healthy children and young adults. Immunosuppressive treatment is usually effective in treating ITP. Many patients with ITP require no emergent treatment. However, the emergency physician should start treatment with a platelet transfusion, corticosteroids, and intravenous immune globulin (IVIG) as soon as the patient with suspected ITP arrives at the ED with serious haemorrhage. The diagnosis is usually made by ruling out all known causes of thrombocytopenia. This review aims to summarize current evidences regarding prevalence, causes, diagnosis and management of immune thrombocytopenia.

Keywords: ITP, Symptoms, Diagnosis, Treatment

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1. INTRODUCTION

Immune thrombocytopenia (ITP) formerly known as immune thrombocytopenic purpura, is an autoimmune syndrome distinguished predominantly by immune-mediated enhanced platelet damage by autoantibodies and inhibited platelet manufacture in the bone marrow in the lead to cutaneal and mucosal bleeding. Also, it was once known as idiopathic thrombocytopenic purpura until it was discovered that the pathophysiology of the thrombocytopenia involved the host immune system. The most important characteristic of this pathology is heightened peripheral destruction of platelets, most patients showing anti-platelet membrane glycoproteins antibodies, platelet destruction via antiplatelet antibodies which may also affect marrow megakaryocytes. ITP is characterized by platelet counts less than 100 × 10^9/L. In ITP, thrombocytopenia happens secondary to antiplatelet antibodies that are produced in the spleen. These antibodies first bind to platelets, followed by phagocytosis of the platelet/antibody complex by the reticuloendothelial system. It represents 0.18 % of all hospital admissions. Patients with ITP appear with a broad variation signs and symptoms ranging from minor mucocutaneous petechiae to severe life-threatening organ bleeding. Patients may present in critical situations, with cutaneous and/or mucous bleeding and conceivably dangerous organ hemorrhages (cerebral, digestive, etc.) Consequently, quick diagnosis and therapeutic involvement are obligatory. ITP has two distinct clinical syndromes, manifesting as an acute condition in children and a chronic condition in adults. Roughly 80% of ITP witnessed in children is acute, adults are usually affected with the chronic form. The disease is thought chronic if the thrombocytopenia continues longer than 6–12 months without another discovered etiology. However, acute ITP naturally resolves within 6–12 months and often happens shortly after an infection or a vaccination. Also, ITP was clinically classified to 3 phases according to an international working group on ITP. Recently identified ITP (newly diagnosed) identifies the first 3 months post-diagnosis. The second phases called Persistent ITP suggests symptoms remaining for 3–12 months. The third phase called Chronic ITP indicates to symptoms long-lasting longer than 12 months. A supplementary phase is called refractory ITP, which consists of cases that fail to resolve with splenectomy and require further therapeutic intervention.

1.1 Prevalence

Immune thrombocytopenic (ITP) is an autoimmune condition that affects nearly 1:10,000 people in the world. The epidemiology of ITP is varied and heterogeneous. ITP affects patients of all genders, races, and ages, it affects both children and adults. The occurrence of ITP is about 1.9–6.4 per 100,000 children per year. Studies from Scandinavia suggest a prevalence of ITP ranging from 4.6 to 5.3 cases per 100,000 children. ITP was present in 9.5 per 100,000 children aged 1 to 5, 7.3 per 100,000 children aged 6 to 10, and 4.1 per 100,000 children aged 11 to 14, according to research that examined data from the Maryland Health Care Commission. In a huge prospective study, 78% of pediatric ITP patients were identified between ages 0–7 with a minor male superiority. According to an analysis of the General Practice Research Database (GPRD) in the United Kingdom (UK), occurrence of ITP was greater in boys between the ages of 2 and 5 (9.7 cases compared to 4.7 cases in girls per 100,000 patient-years, respectively) compared to that in teenagers between ages 13–17 (2.4 cases per 100,000 patient-years, with equal sex distribution). Depending on adults, one large review of published articles reported the incidence of ITP to be around 3.3 per 100,000 per year. Primary ITP has a prevalence of 9.5:100,000 in adults with an occurrence of 3.3:100,000 per year. As ITP is commonly a chronic disease in adults, the prevalence is greater than the incidence, and one study described the prevalence of ITP to be 12.1 per 100,000 adults per year. A prospective, population-based study of patients older than 16 years old with newly diagnosed ITP revealed an annual report incidence 1.6 cases per 100,000; the incidence was a little greater in females between 45–49 years but otherwise no gender differences existed. A Scandinavian study discovered an ITP incidence of between 2.25 and 2.68 per 100,000 individuals/year; the incidence was greater in females (male ratio 1.7) and the elderly. Additional reports have indicated a prevalence of ITP in adults ranging from 4.0 to 23.6/100,000 patient years. Generally, the male to female ratio in children decreases with increasing age, and reverses in adulthood. Female preponderance is clearly recognized in adults with ITP. Increased general occurrence of autoimmune diseases in adult females is believed to be a factor. Together male and female incidence of ITP increases with increasing age.

1.2 Causes

The pathogenesis of ITP includes harm of tolerance to glycoproteins expressed on platelets and megakaryocytes. ITP develops by two processes either immune-mediated increased destruction of platelets or decreased production of platelets that leading to a complete reduction in circulating platelets. Generally, Immune thrombocytopenia (ITP) is idiopathic in 80% of cases, and primary ITP is often supposed of as an autoimmune disorder due to pathogenic anti-platelet autoantibodies, T cell-facilitated platelet destruction and decreased megakaryocyte (MK) function. Nevertheless, 20% of cases of ITP can existing secondary to other causes. Viral infections containing human immunodeficiency virus (HIV), hepatitis C virus (HCV), cytomegalovirus (CMV), varicella zoster virus (VZV), auto immune diseases such as systemic lupus erythematosus (SLE) and lymphoproliferative disorders like chronic lymphocytic leukemia (CLL) are the most common causes of secondary autoimmune platelet destruction. In the infectious cases, it might be that a viral antigen is familiar as being like a platelet antigen, a process called molecular mimicry, which afterward gives rise to cross-reactive anti-platelet autoantibodies. In the case of thrombocytopenia related to drug exposure (with the exclusion of myelosuppressive chemotherapy), the term “drug-induced” was preferred. Quinine was the first drug to be identified as causing immune-mediated thrombocytopenia. Some more widely used medications that are known to cause drug-induced immune thrombocytopenia include carbamazepine, ceftriaxone, ibuprofen, mirtazapine, penicillin, trimethoprim-sulfamethoxazole, and vancomycin.

1.3 Clinical presentation and symptoms

Patients with ITP present with a wide variety signs and symptoms ranging from minor mucocutaneous petechiae to severe life-threatening organ bleeding. The symptoms of ITP are reliant upon the intensity of thrombocytopenia. Signs and symptoms usually begin appearing with platelet counts less than 100 × 10^9/L, but bleeding is extraordinary till platelet counts decline lower than 30 × 10^9/L. Platelet counts below 20% of cases of ITP can existing secondary to other causes.
20,000/μl; I raise the risk of spontaneous bleeding like epistaxis or gum hemorrhage and menorrhagia, petechiae or ecchymoses, especially at the extremities. Mucosal bleeding may occur under 10,000/μl; the bleeding time also grows while dangerous hemorrhagic cases such as intracranial, intestinal, or other internal bleeding typically occurs with platelet counts less than 10 × 10^3. Outside of bleeding-related symptoms, a couple of other symptoms are worth mentioning. Fatigue is a frequent symptom in both adults and pediatric patients with ITP which appearing in roughly 22% of children, and 22 to 39% of adults. Whereas the primary symptoms of ITP include bleeding, thrombosis is more popular in patients with ITP as compared to controls. Numerous patients with ITP are symptomless, and their decreased platelet count is often noticed parenthetically.

### 1.4 Pathophysiology

Our knowledge of the pathophysiology of ITP has considerably increased during the past several years. The thrombocytopenia caused by pathologic antiplatelet antibodies, defective megakaryocytopoiesis, and T-cell-mediated destruction of platelets, each of which plays a different role in each patient with Primary ITP, is now understood to be an acquired immunological illness. Other underlying conditions including autoimmune disease (systemic lupus erythematosus or rheumatoid arthritis), HIV, Helicobacter pylori, or immunological dysregulation syndromes like common variable immunodeficiency are linked to secondary ITP. Approximately 80% of persons with ITP have main ITP. Although certain patients with secondary ITP and severe disease may need ITP-like therapy to stabilize the platelet count while other treatment is started, secondary ITP treatment and pathophysiology are typically centered on the underlying disorder and are not the focus of this article. The evidence also implies that many ITP patients have poor platelet production. Megakaryocytes from ITP patients are aberrant, and electron microscopic changes in cell culture with ITP plasma revealed improper apoptosis and hindered megakaryocyte proliferation. Additionally, the serum thrombopoietin levels in ITP patients are hardly ever high. These data are somewhat validated by the fact that TPO receptor agonists are effective.

### 1.5 Diagnosis

The diagnosis of Immune thrombocytopenia ITP is one of exclusion. It is characterized by isolated thrombocytopenia, with normal morphology and else normal CBC. Corresponding to an International Working Group consensus panel of both adult and pediatric experts, ITP is characterized as a platelet count less than 100 × 10^9/L in the absence of other causes of thrombocytopenia. Diagnosis of ITP is validated by a discovering of thrombocytopenia in a blood smear. A sensible examination of the peripheral blood smear (PBS) is essential to eliminate other reasons of thrombocytopenia, such as the microangiopathic disorders, platelet satellitism or pseudo thrombocytopenia. Bone marrow examination is not commonly required in ITP. It is recommended to be performed if another hematological pathology is suspected (other anomalies on the CBC, unexpected systemic signs, and symptoms, such as adenopathies, organ enlargement, etc.), if patients are over 60 years old, and before splenectomy. Furthermore, amongst patients with ITP, it is essential to differentiate primary and secondary ITP. In particular, the physician should completely review the patient's recent medications as drug-induced immune thrombocytopenia is often clinically undifferentiated from primary ITP, so it may be ignored even if the suitable diagnostic tests are required. Generally, Primary ITP is a diagnosis of exclusion by carefully ruling out causes of pseudo thrombocytopenia, secondary ITP, and inherited ITP. Getting a precise history come together with a complete blood count and a thorough evaluation of the blood smear is the first and most important step. Harmonizing nomenclature and terminologies for ITP has advanced significantly in recent years, allowing recommendations to be made that are applicable to many ITP patients. The best way to manage patients is questionable, however, due to considerable gaps in the information that is currently accessible (such as the absence of information or a lack of agreement on second-line medicines and best practises for managing chronic ITP). The assessment of a peripheral smear, appraisal of the patient's history, and physical examination are typically used to make the diagnosis of ITP. All ITP patients should undergo a few extra tests, according the IWG's recommendations, including tests for hepatitis C, HIV, H pylori, direct antiglobulin, and blood type. Similar testing, with the exception of H pylori testing, is advised by the ASH recommendations for adults with ITP (only recommended for some geographic areas and if treatment of eradication is possible). The ASH guidelines suggest that bone marrow tests may not be necessary in any patient population, which is supported by some population studies, in contrast to the recommendations made by the IWG to perform bone marrow investigations in patients >60 years old with newly diagnosed ITP.

### 1.6 Examples of Utility of various evaluations in the diagnosis of ITP

#### Basic evaluation (Patient/family history)
- Tests of potential utility (Glycoprotein-specific antibody), Tests of unproven benefit (Thrombopoietin)

#### Basic evaluation (Physical examination)
- Tests of potential utility (Antiphospholipid antibodies (including anticardiolipin and lupus anticoagulant), Tests of unproven benefit (Reticulated platelets)

#### Basic evaluation (Complete blood count and reticulocyte count)
- Tests of potential utility (Antithyroid antibodies and thyroid function), Tests of unproven benefit (Platelet-associated immunoglobulin G)

#### Basic evaluation (Peripheral blood film)
- Tests of potential utility (Pregnancy test in women of childbearing potential), Tests of unproven benefit (Bleeding time)

#### Basic evaluation (Quantitative immunoglobulin level measurement)
- Tests of potential utility (Antinuclear antibodies), Tests of unproven benefit (Platelet survival study)

#### Basic evaluation (Bone marrow examination (in selected patients)
Tests of potential utility (Viral PCR for parvovirus and CMV), Tests of unproven benefit (Serum complement) 46

1.7 Treatment

The most important objective for treatment of ITP is to provide a safe platelet count (e.g., one that prevents major bleeding) rather than improving the platelet count to normal levels. 48 Treatment of patients with ITP should consider the seriousness of the illness and the age of the patient because the bleeding risk and the hemorrhagic fatality rate increase with age. 32 Recent guidelines recommend that treatment should be introduced in the occurrence of bleeding symptoms. 49 Treatment is usually reserved for those with symptomatic ITP. The target is to achieve a hemostatic platelet count, which is around 20-30 x 10^9/L, while this differs by person. Most ITP cases are self-limiting and need no treatment because most often the event responsible for antiplatelet antibody production is a viral illness. At present, most treatment protocols focus on the diminution of platelet destruction, and the drugs used are usually immunosuppressives. 50 Treatment of ITP can be divided into medical and surgical management. Medical management is further divided into first line and second-line pharmacotherapy. Medical options for front-line drug therapy are corticosteroids, intravenous (IV) immunoglobulin (Ig), and IV Rh anti-D. 54 Corticosteroids are the most extensively used treatment. Firstly, at least 80% of the ITP patients respond, a high percentage of patients decline when attempting to reduce the corticosteroid doses. 37 Dexamethasone and prednisone have been shown to modulate B-cell and dendritic cell activation, leading to a decrease in immune-mediated destruction of platelets. 12 In steroid-resistant patients, the addition of intravenous immunoglobulin (IVIG) or Rh (D) immune globulin (anti-RhD) can be used to improve the treatment effect. Furthermore, these two treatments can be used in patients when corticosteroids are contraindicated. 51 IVIG is also suggested when platelet counts need to be increased quickly, such as in cases of active and severe bleeding, and can be used in combination with corticosteroids in select patients. Anti-RhD can be useful in combination with corticosteroids in patients who are RhD positive. 50 If patients with ITP fail first-line treatments or relapse, second-line treatments are required to control the disease. Second-line therapies involve splenectomy and/or immune-suppressive agents such as the B cell-depleting anti-CD20 agent Rituximab. 37 In fact, the ASH 2011 guidelines still suggest splenectomy as the next option in therapy after failure of remission with corticosteroids, IVIG, and anti-RhD. 51 Splenectomy is still the golden model for repairing physiological platelet counts in patients with ITP, and it persists the method of choice in refractory patients with ITP. 52, monoclonal antibody against the CD20 antigen (anti-CD20), rituximab, is one new choice for the treatment of chronic and persistent ITP. It is supposed to cause either B cell apoptosis or destruction in the spleen via either complement-dependent cytotoxicity or antibody-dependent cellular cytotoxicity (ADCC). The resulting depletion of B cells results in decreases of anti-platelet antibody titters and, remarkably, in the normalization of the T cell impairments detected in patients with chronic ITP. 53, 54 Patients who fail splenectomy or Rituximab can be treated with TPO-receptor agonists. Both Eltrombopag and Romiplostim activate TPO receptors on MKs and induce platelet production via the JAK2 and STAT5 kinase pathways, and both therapies have proven efficacious in most refractory patients with ITP. 55, 56 Whether an ITP is primary or secondary affects how it is managed. We will talk about possible treatments in the remaining portion of this section for either primary or secondary ITP. If a patient has secondary ITP, addressing the underlying condition or stopping the medicine it was caused by is crucial. Regardless of the ITP’s underlying cause, the aim of treatment is to stop or stop substantial bleeding, not to return the platelet count to normal. In the ED, this is especially true. Due to the paucity of significant randomised trials, the treatment of ITP is mostly relied on low quality evidence and expert opinion. As a result, we manage ITP in accordance with the 2019 American Society of Hematology clinical practise recommendations and a 2019 global consensus report. 37, 58 Treatment Strategies for ITP Based on Platelet Count and Symptoms. These Recommendations are Primarily Based on the 2019 Clinical Practice Guidelines from the American Society of Hematology and a 2019 International Consensus Report. 59, 60

-Platelet Count (>30 x 10^9/L) Symptoms (None or minor mucocutaneous bleeding), ED Treatment (No medications; counsel patient to avoid medications or activities that increase bleeding risk.)

-Platelet Count (20–30 x 10^9/L) Symptoms (None or minor mucocutaneous bleeding), ED Treatment (Consider corticosteroids; consult hematologist.)

-Platelet Count (<20 x 10^9/L) Symptoms (None or minor mucocutaneous bleeding), ED Treatment (Consult hematologist,Adults: Corticosteroids,Children: Consider corticosteroids.)

-Platelet Count (<20 x 10^9/L) Symptoms (Severe (but not critical) bleeding),ED Treatment (Corticosteroids and IVIG; consider platelet transfusion; consult hematologist.)

-Platelet Count (<20 x 10^9/L) Symptoms (Critical bleeding),ED Treatment (Corticosteroids and IVIG; platelet transfusion; consult hematologist)

1.8 Emergency Treatment of ITP

Patients with dangerous thrombocytopenia, especially those with newly diagnosed ITP should be hospitalized. The aim of therapy is to enhance the platelet value as soon as possible. Corticotherapy or immunoglobulins are administered IV. Platelet transfusion provides transient increases in the platelet count in emergent situations, and concurrent infusion of IV Ig may prolong survival of transfused platelets in some patients. 61 In some patients, the life span of the transfused platelets can be raised by the simultaneous administration of immunoglobulins. 62 To increase the platelet number very rapidly, splenectomy may be used; it was performed as an ITP treatment method in patients with severe intracranial hemorrhage. 63
Diagnostic Tests to Avoid or Defer in the ED

In general, no additional testing in the ED is necessary if the diagnostic tests are compatible with main ITP. Antiplatelet antibody testing is one particular procedure to avoid in the ED. The sensitivity of antiplatelet antibody testing was reported to be 53% in a prospective research intended to find platelet-bound autoantibodies reactive against GPs IIb/IIIa, Ib/IX, or Ia/IIa; this is probably too low for the test to be effective. Furthermore, while bone marrow testing may occasionally be used to rule out malignancy or myelodysplastic syndrome in atypical or resistant instances of suspected ITP, it is not advised in the vast majority of cases and does not need to be scheduled in the ED. Immunologic tests (like antinuclear antibodies) may be beneficial for patients with joint pain, malar rash, or other symptoms that could indicate a rheumatologic condition, but since a definitive diagnosis of a rheumatologic condition in the ED is unlikely, it may be best for the emergency physician to defer immunologic tests to the outpatient setting or a specialist.

Symptoms Not Due to Bleeding

There are a few additional symptoms worth addressing in addition to those connected to bleeding. Both adult and juvenile ITP patients commonly experience fatigue, but adults are more likely to experience it. According to one study, fatigue was the most prevalent symptom and was experienced by 58% of adult patients who had been diagnosed with ITP more than a month after the onset of symptoms. In the meantime, 22% of paediatric patients are said to experience weariness. Although bleeding is one of the main symptoms of ITP, people with ITP have a higher rate of thrombosis than controls. Because thrombosis in ITP is still quite uncommon, the emergency physician should refrain from looking for it unless there is a clinical suspicion of it. Patients with ITP have a 1.5-fold higher overall mortality rate compared to the general population, as well as a noticeably higher risk of infection.

ITP in Pregnancy

With an estimated incidence of 1 in 1000 to 1 in 10,000 pregnancies, ITP can develop during pregnancy. Low platelet counts in pregnancy are still most frequently caused by gestational thrombocytopenia (GT), which can be challenging to distinguish from ITP. Both conditions are exclusion diagnoses, but GT’s platelet count seldom dips below 70 10^9/L and often does not result in bleeding. ITP, on the other hand, raises the risk of maternal and newborn haemorrhage and can result in a significantly decreased platelet count. When patients are treated appropriately medically, cases of maternal or neonatal haemorrhage are uncommon. The incidence of foetal loss appears to be higher in women with ITP who are diagnosed before becoming pregnant (11.2% vs. 3.9% in women diagnosed during pregnancy), and the foetal birth weight appears to be lower (17.9% vs. 9.7%). Premature birth rates have also reportedly increased.

Thrombocytopenia

Patients with COVID-19 may experience pharmaceutical side effects, sepsis, or disseminated intravascular coagulation that results in thrombocytopenia. Furthermore, COVID-19 is now a well-researched cause of ITP. Bhattacharjee and Banerjee reported that 71% of COVID-19-induced ITP was detected in elderly individuals, and that moderate to severe COVID-19 was present in 75% of cases. The platelet count often does not drop below 100 10^9/L in COVID-19 patients with thrombocytopenia. Severe bleeding has been rare in affected people, despite reduced platelet counts being linked to an increased risk of mortality and severe illness in COVID-19 patients. The vast majority of COVID-19-related ITP cases have good prognoses, and the majority of patients respond favourably to the typical ITP therapies outlined below.

CONCLUSION

Immune thrombocytopenia can be diagnosed at any age; however, it is most common in early childhood and late adulthood. Platelet levels are frequently reduced abruptly, but they normally return to normal within weeks to months. The majority of children experience spontaneous remission within a few weeks or months, and splenectomy is rarely required. However, spontaneous remissions necessitating splenectomy in young adults are uncommon in the first several months following diagnosis.
CONFLICT OF INTEREST

Conflict of interest declared none.


