

## The Cause and Effect of Immune Thrombocytopenia (ITP) on Individuals

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Received: 07 Mar 2023; Accepted: 10 Apr 2023; Published: 15 Apr 2023

**Citation:** Thomas M, Gallicchio VS. The Cause and Effect of Immune Thrombocytopenia (ITP) on Individuals. J Med - Clin Res & Rev. 2023; 7(4): 1-11.

### ABSTRACT

*Immune thrombocytopenia is a rare blood disorder in which an individual has a decreased level of platelets due to the immune system destroying the blood-clotting platelets. Platelets function in the body to help clot the blood, but in people with ITP, the body produces antibodies that disrupt and attack the creation, leading to lower levels. The average platelet count ranges from 150,000-400,000 per microliter of blood, but in individuals with ITP, the platelet count is less than 100,000 [1]. This significant decrease in platelet count can cause easy bruising, bleeding, and fatigue, among various symptoms that can disrupt an individual's life. The current diagnosis of ITP is centered on presumptions and excludes other causes of thrombocytopenia due to a variety of acquired and inherited that can present similar symptoms. In some cases, ITP may not cause symptoms, and for most children and adults, ITP is not severe. Acute ITP will typically go away on its own without the need for extensive therapy. In individuals with more advanced cases, or chronic ITP, one may receive a wide range of treatments. The stage of the disorder, current medical history, and genetics all have significant roles in determining the treatment an individual will receive.*

### Keywords

Immuno thrombocytopenia, Immune response.

### List of Abbreviations

CBC: Complete blood count; Fc: Fragment, crystallizable; Hb: Hemoglobin; HCV: Hepatitis C; HDD: High-dose dexamethasone; HRQoL: Health related quality of life; HIV: Human immunodeficiency virus; IgG: Immunoglobulin G; IV: Intravenous; ITP: Immune Thrombocytopenia; Kg: Kilogram; L: Liter; MCAT: Medical College Admission Test; Mg: Milligram; NSAIDs: Non-steroid anti-inflammatory drugs; PRO: Patient report outcome; QoL: Quality of life; SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2; SLE: Systematic lupus erythematosus; TAR: Thrombocytopenia-absent radius; TTP: Thrombotic thrombocytopenia purpura; TPO-RA: Thrombopoietin-Receptor Agonists;  $\mu$ L: Microliter; WBC: White blood cell.

### Introduction

Immune thrombocytopenia, or ITP, is an autoimmune disorder classified by decreased platelets within the blood. Platelets are

specialized blood cells within the body that originate from bone marrow and circulate to bind together when the body recognizes a damaged blood vessel [2]. Platelet function is to form a clot around a damaged vessel to prevent further bleeding in the individual. An average platelet count consists of 150,000-450,000 per microliter of blood. It is crucial to note that excessive bleeding typically only occurs once platelet levels have reached less than 50,000 per microliter of blood. A platelet count lower than the normal range is called Thrombocytopenia [1]. Purpura refers to the purple-colored blood spots that can be spotted on an individual due to the bursting of small blood vessels. Purple bruising and excessive bleeding are two significant indicators of a low platelet count within a patient [3].

Currently, it is estimated that there are 200,000 individuals worldwide living with ITP and 50,000 present within the United States. A study that examined the incidence rates of immune thrombocytopenia stated “while reports of ITP are highly variable, the most robust estimate of acute ITP in children ages from 1-5 is 9.5 per 100,000 children a year, 7.3 per 100,000 children ages from 6-10, and 4.1 per 100,000 children ages eleven to fourteen.

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The strongest estimate of acute ITP in adults is 3.3 per 100,000 adults a year [4]. While ITP can occur at any age and is highly variable in whom it affects, it has been reported that more than 40% of all cases occur in individuals younger than ten years old. The highest incidence rate is reported in children aged two to four. There is limited variability between males and females in the cases reported until the adolescent stage is reached. After this period, ITP is diagnosed more commonly in females, with the highest prevalence of cases being in adults over sixty.

### **The Symptoms of ITP**

Symptoms of immune thrombocytopenia are variable and typically conflict with those of other blood disorders. Currently, no single laboratory test is a solid indicator that one is suffering from ITP. Immune thrombocytopenia is usually diagnosed through diagnosis exclusion, where other disorders have been considered and eliminated based on factors such as the severity of the case, family history, and symptoms [5]. Typical symptoms reported from those diagnosed with ITP consist of bleeding for long periods, especially within the gums, nose, and after a minor injury, easy bruising, extreme fatigue, heavy menstrual periods, petechiae, purpura, confusion, and an enlarged spleen or liver [3]. Individuals may develop symptoms rapidly and unexpectedly, commonly through abnormal bleeding, bruising, or petechiae, characterized by small red dots on the skin. More significant symptoms can also occur suddenly, consisting of bleeding from the mouth or nose and within the urinary tract. This is especially dangerous to menstruating women as this can result in low levels of blood cells circulating within the system, causing an excess amount of bleeding within the individual. Extreme life-threatening symptoms such as internal bleeding and bleeding within the brain, known as an intracranial hemorrhage, are uncommon but have been found in several untreated cases. It is essential to state that some individuals may be asymptomatic. Patients will typically become aware of their abnormal platelet count following a routine laboratory screening, before a procedure, or during pregnancy. Overall, symptoms in children are reported to be similar in adults. Children typically have lower platelet counts than adults and experience more bleeding within the mouth and more purpura and petechiae. More children are prone to presenting as asymptomatic as adults with ITP have a higher rate of experiencing extreme life-threatening symptoms.

### **The Treatment of ITP**

Treatment of immune thrombocytopenia is highly subjective to the individual and varies on a case-to-case basis. Individuals suffering from mild cases may only require routine monitoring and regular platelet checks through laboratory screenings. More comprehensive approaches may be required for older individuals and those experiencing chronic or more severe cases. Typically, this circumstance applies to older adults as most children can recover without treatment over time. Inhibiting medication that alters platelet function is one of the first steps in controlling ITP. Over-the-counter medications such as aspirin, ibuprofen, and ginkgo biloba should be seized or taken in minimal quantities [3].

In most cases, prescription medication may be given to the individual by a treating physician [5]. An oral corticosteroid, a steroid such as prednisone, is commonly the first medicine that physicians will provide. Steroids are similar to the hormone produced by the adrenal gland and help slow down the breakdown of the platelets within the body. Steroids should not be consumed for long as they can have highly adverse effects. Most individuals take the steroid as a pill for two to four weeks and slowly lower the dose until the medicine is complete. In case of dangerous bleeding or an immediate need for platelet increase, an intravenous immune globulin can be administered. Immune globulins, also known as antibodies, are found within the blood, and used by the immune system to recognize bacteria and viruses. Antibodies can halt the destruction of platelets by the spleen, increasing overall platelet count. Intravenous immune globulin is a short-term resolution; the effects typically last a few weeks. Anti-RhoD is another form of immune globulin that can be prescribed. This form of antibody is more cost and time efficient than intravenous immune globulin. The immune globulin goes against the D antigen of the Rh blood group and inhibits the destruction of antibody-coated platelets by working through Fc receptors on macrophages by using anti-D-coated erythrocytes. For this process to work, individuals must be Rh-positive and have a functional spleen [6]. Once it is determined that the patient has the protein, Rh factor, anti-D can be prescribed and significantly increase the number of platelets in circulation. The response rate using Anti-D immunoglobulin has been reported to be around 65%; however, there is a low incidence rate, and concern about intravascular hemolysis has been documented. Thrombopoietin-Receptor Agonists such as avatrombopag, eltrombopag, and romiplostim are other medications that may be prescribed to an individual are currently the three drugs that have been approved by the U.S. Food and Drug Administration for treatment of chronic ITP. This drug class is used to help bone marrow boost platelet production by enhancing the function of the immune system. Eltrombopag is a manufactured non-peptide molecule that is taken orally in a dose of 25 mg. The typical dose begins at 50 mg but may be increased to 75 mg to maintain platelet count. Reports of patients that have taken Eltrombopag have had a promising platelet response between a 59-79% increase; however, unwanted side effects have been a cause for concern [7]. Romiplostim is a peptide Thrombopoietin-Receptor Agonist that is given to patients through injection at a weekly basis with a starting dose of 1 mg/kg but can be increased to a maximum dosage of 10 mg/kg. In trials looking at the response rate in individuals given the subcutaneous injection, the platelet response rate was 71-92%, and the long-term response was 38-56% [8]. Avatrombopag is an oral molecule TPO-RA that has been approved for the treatment of chronic ITP as well as those suffering from liver disease. This is considered the most flexible TPO-RA as there are fewer restrictions and adjustments that patients have to endure while receiving treatment [9]. Other medications, such as Rituximab and Truxima, may be prescribed as a last option and are used to increase platelet count by limiting the immune response involved in destruction [10]. Surgery may be the recommended action if drug intervention is unsuccessful, or the patient's case

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is severe. A splenectomy will immediately eliminate the leading cause of platelet destruction within the body. The spleen is the major organ that is responsible for platelet destruction and serves as the site of anti-platelet antibody production [11]. This form of treatment should be advised on the side of caution and is only used following the failure of multiple medical treatments, as living without a spleen places the patient at a high susceptibility for infection for their lifetime. Recently, laparoscopic splenectomy has been chosen over an open splenectomy due to the risk of complications and higher rates of sepsis and infection within patients [12]. However, it has been reported that approximately 70-80% of chronic ITP patients that have received a splenectomy have sustained remission for more than six months, and 60-70% have sustained remission for over five years [11].

### **The Different Forms of ITP**

The population's two prevalent forms of ITP are acute thrombocytopenia and chronic thrombocytopenia. Acute thrombocytopenia purpura is common in young children ages two to six. Although reported numbers are low, it is still possible for acute ATP to occur in adolescents and adults. Acute ITP typically presents itself following a viral infection. Symptoms of acute ITP are reported as sudden yet mild and usually disappear after a few months without the intervention of medical treatment. Like acute ITP, chronic ITP can occur at any age but is more prevalent in adults and adolescents than children. Symptoms can occur suddenly and last at least six months, years, to a lifetime. Chronic ITP is reported more in females in comparison to males. This form of ITP has the potential for often reoccurrence and may require frequent medical intervention and care with a hematologist [13]. Lifetime monitoring and future care is almost guaranteed in chronic ITP cases due to the likelihood of remission.

### **Discussion**

Immune thrombocytopenia is one of the most prevalent bleeding disorders diagnosed within the population. ITP was initially discovered in the 1500s when a boy presented dark circles on the skin resembling fleabites, with no fever and blood discharge. At the time, physicians were unaware of the cause of the boy's symptoms; however, he quickly recovered after several days. About two centuries later, Dr. Paul Gottlieb Werlhof, a German physician, came in contact with another ITP patient and named the disorder *Morbus Maculosus Hemorrhagicus*, with hemorrhage referring to the bleeding within patients. The name was shortly changed to *M. Maculosus Werlhofi*, as it was discovered that bleeding was not the prominent symptom shown in all patients. In the 19th century, the platelet was recognized, leading to the discovery of the thrombocytopenic component of ITP. In the 20th century, the disorder's pathophysiology led physicians to investigate treatment options, new therapies, and the underlying cause of the disease [14]. In today's day in age, ITP is known as "idiopathic thrombocytopenic purpura." However, the Internal Working Group has suggested the disorder's name be altered to "Immune Thrombocytopenia," with the abbreviation "ITP" to be maintained. This change is due to many diagnosed individuals lacking purpura as a symptom of their condition [15]. ITP is

characterized by a low platelet count, bruising, and hemorrhagic episodes due to antiplatelet autoantibodies. ITP is mediated by platelet autoantibodies that destroy platelet antibodies and inhibit the manufacture of the body's production. Platelets are needed within the body to maintain the integrity of the vascular walls by adhering to coagulation proteins, which allow them to attach to vascular walls when there is an injury to stop the bleeding. IgG help circulate the remaining platelets, which cause the body to accelerate the removal of these cells through macrophages of the spleen, and in some case, through the liver. Bone marrow aids in production by increasing platelet production [16]. In its primary form, ITP is idiopathic and is the absence of other disorders that cause thrombocytopenia. An individual with primary form has a platelet count less than  $100 \times 10^9/L$ . ITP can occur post viral infections or alongside other viral infections such as human immunodeficiency virus. It can also appear alongside cancers such as lymphoma or adenocarcinoma and other autoimmune diseases such as thyroid disease and autoimmune hepatitis. Diagnosis of ITP is complicated due to its presence being highly similar to those in chronic lymphocytic leukemia, lymphomas, SLE, infectious mononucleosis, and other bacterial infections. In most of these diseases, especially within ITP, antiplatelet formation leads to the destruction of platelets within the body. In ITP, the immune system directly destroys platelets, and in some cases, T cells will directly attack platelets, causing a substantial decrease in the amount within circulation in the body. While the underlying cause is unknown, it is suspected that the immune system resorts to destruction due to medications, infections, pregnancy, other immune disorders, or cancers. ITP frequently is most commonly found in young adults. Regarding chronic ITP, women between the ages of thirty and forty are more affected, encompassing a ratio of 3-4 to 1 compared to their male counterparts. It is suspected that sex hormones play a role in women's susceptibility to ITP. In response to ITP treatment, women and men have reported having variations in the reaction, which also may be linked to the sex hormone as this hormone has a prominent influence on drug absorption, distribution, metabolism, and pharmacodynamics [17]. There is no single treatment that works best for every individual, so physicians take a wide variety of factors into consideration. These factors include age, overall medical history, risk, disease extent, medication tolerance, and expectation of remission [13].

### **Acute ITP Compared to Chronic ITP**

Two different clinical forms that ITP can be diagnosed consist of an acute condition and a chronic condition. The Internal Working Group on ITP has broken down the disorder into clinical phases consisting of newly diagnosed ITP being the first three months post-diagnosis, persistent ITP for three to twelve months, chronic ITP greater than twelve months, and refractory ITP as the last stage, defined as the failure of splenectomy [18]. The acute form of ITP is typically present in childhood, typically age's two to six, and is common in both sexes. Chronic ITP is seen more in adults, especially in females. The onset of bleeding within acute ITP is severe, whereas chronic is slower and much more controlled. In acute ITP, the autoantibody binds to platelet, and the destruction is done by splenic macrophages. In chronic ITP, specific

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autoantibodies called IgG bind to particular glycoproteins, and various processes cause platelet destruction within the body. Acute ITP is broken down into primary and secondary forms. Primary ITP is the most common form presented in children and has no determined cause. Secondary ITP has a known cause, typically due to another autoimmune disease, viral infections, drugs, and vaccines. The symptoms of acute ITP in children usually follow the presentation of a common viral illness. Infections that are closely linked with ITP are HIV, HCV, and *H. pylori*. Some patients may present with excessive bruising, oral bleeding, menorrhagia, and hematuria, which are common in other illnesses. Due to the similarity in presentation, a diagnosis exclusion is used before diagnosing acute ITP or chronic ITP. The most common diagnostic techniques consist of a peripheral blood smear, complete blood count, and bone marrow aspiration. Physicians may look at white blood cell numbers to rule out bone marrow suppression due to viral infections or drugs. The peripheral blood smear of individuals with ITP will typically present with abnormal red blood cells, usually showing anemia, a normal Hb, normal WBCs, and decreased platelet count. If the ITP is caused by a viral illness, there may be an atypical number of lymphocytes present. Clumps of platelets due to ethylenediaminetetraacetic acid is an indicator of pseudo thrombocytopenia. The diagnosis may be confirmed once repeated on heparin-anticoagulated or citric-anticoagulated blood. A Bone marrow aspiration could be completed and examined for leukemia or a metastatic tumor. The bone marrow may present with abundant megakaryocytes and an abnormal shape. It is also possible that the bone marrow may have hypercellular erythroid hyperplasia. Genetic disorders such as Bernard-Soulier, Type II-B von Willebrand disease, and Thrombocytopenia-absent radius (TAR) syndrome must all be excluded from the final diagnosis. A laboratory examination of a CBC with differential and reticulocyte count is necessary for determining the final diagnosis [19].

### **The Difference in ITP Presentation in Adults Compared To Children**

Adults and children can both be diagnosed using diagnostic exclusion, but the type of first-line therapies vary due to the severity of the case and patient history. Due to the greater chance of spontaneous remission in children, observation is currently the leading form of treatment for diagnosed children [16]. Some children have been reported to of recovered in as little as three months. Children with acute ITP will only be referred to a pediatric hematologist if more than one blood cell line is low or if blasts are present on the smear. Other indicators warrant a referral consisting of a positive direct Coombs test if the child fails treatment for the ITP. Data has shown that 85% of children have an unharmed form of ITP and can recover without medical intervention. The treatment raises the platelet count to a "normal" range level. Severe bleeding is highly unusual in children with acute forms of ITP. Reports have indicated that severe bleeding occurs in less than 1% of children with a platelet count of less than twenty thousand [19]. It has been reported that less than 10% of children develop chronic ITP [16]. In most chronic ITP cases, the onset of symptoms is gradual and can occur in any individual at any age lasting a minimum of six

months to a lifetime. Older adults, specifically females, are the most commonly reported individuals to develop chronic ITP. Symptoms such as bruising, nosebleeds, petechiae, blood in the urine or stool, and extreme fatigue are present in chronic ITP patients. The symptoms vary in severity to the individual but are typically more manageable compared to acute ITP cases. This is due to the sudden onset of acute ITP that can cause extreme symptoms for a short period of time. The goal in chronic ITP cases is to increase the platelet count that prevents extensive bleeding instead of reaching the normal range, as in treating acute ITP. A positive response is typically achieved in most ITP cases following the first treatment, yet some patients may require additional rounds over time. Chronic ITP patient that has reached a level of 30,000/ $\mu$ L to 50,000/ $\mu$ L may just be monitored for future symptoms as drops in platelet counts have been reported. A platelet count of 20,000/ $\mu$ L to 30,000/ $\mu$ L is the threshold that deems major bleeding possible. In some chronic ITP cases, the decision to perform a splenectomy may be the chosen course of action based on the current nature and severity of bleeding and the risk of significant bleeding in the future. This treatment only occurs once the first line of treatment is unsuccessful and spontaneous recovery is ruled unlikely [20]. Due to the unpredicted nature of ITP, treatment is still not curative, so even when remission is likely, relapses can occur. The primary goal of therapy in both cases is to reduce the severity of bleeding to ease the concern of excessive bleeding so patients can live a relatively everyday life. The risk for bleeding is low compared to other disorders that cause thrombocytopenia. Even in individuals who have extremely low counts, extreme bleeding is typically not presented until after other symptoms are significant. However, this excludes situations where an individual is put at risk of an accident or injury; in that case, severe bleeding poses a considerable risk.

### **Refractory ITP**

In some cases, patients will have an adverse or unresponsive reaction to conventional treatments, placing their diagnosis into the refractory ITP category. The American Society of Hematology Guidelines has reported that the refractory stage of ITP is the definition of identifying the most severely affected patients. This is because patients in this category of ITP do not have a significant enough response to treatment or relapse after splenectomy. In this case, the individual may still require treatment due to significant bleeding, however, options are limited due to severity. Due to the lack of advancement in ITP treatment, the "curing" therapy is considered a splenectomy; however, patients who still suffer post-surgery have ITP characterized as pertinent. The refractory stage is paired with the worsening of QoL and is very difficult to diagnose and treat with physicians. As in all forms of ITP, the clinical treatment is inconsistent. However, recent studies have shown that combining therapeutic practices targeting various biological processes has yielded positive results. A study examining current strategies for treating and managing refractory ITP found that 10% of patients become unresponsive to treatments within one year [21]. Extensive laboratory workup is necessary to rule out other underlying diseases such as myelodysplastic syndrome, drug-induced thrombocytopenia, and bone marrow syndromes. Different

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therapy may be paired together to help treat the symptoms of refractory ITP, as typically, there is a pattern of consistent failure with the use of one treatment. The availability of new research into drugs such as rituximab, TPO-Ras, and fostamatinib has shown the possibility that some relief may be feasible for individuals suffering from long-term ITP [22].

### **Treatment of ITP in adults Compared to Children**

There is a clear-cut difference in the standard protocol enforced when treating children with ITP and adults with ITP. Typically, children have fewer symptoms presentation and a decreased likelihood of spontaneous remission than older adults. Two major factors were researched in the difference between children and adult ITP cases. The first factor examined the differences in symptoms in males and females in acute and chronic ITP. The other factor analyzed comorbid medical conditions in diagnosed adults, typically presenting with chronic ITP. Among the adults affected, females have a higher predominance rate, encompassing a 2:1 ratio, of all adults diagnosed. There is no confirmation as to why females have a greater chance of receiving a diagnosis of ITP. The diagnosis may be caused by the recently reported increase in autoimmune disease in females. Acute ITP has been shown to affect all genders at the same rate similarly. In children, boys are typically diagnosed more than their female counterparts. Within the overall population of adults affected by ITP, there is an upward trend in comorbid medical conditions such as diabetes, gastrointestinal disease, hypertension, and thyroid disease. Data collected from the Pediatric and Adult Registry on Chronic ITP showed that comorbid disease is 3.9% in children compared to 30% in adults [23]. The sample was evaluated two years later, and children showed an incidence rate of 10.7% and 30.7% in adults showing an upward increase as age increased [24]. One significant difference in the variability in treatment for adults compared to children is that children can often receive spontaneous remission without extensive medical treatment. Guidelines developed by the American Society of Hematology for treating ITP were created through evidence-based practice from 1928 through 1989. During this time, it was discovered that, in most cases, adults with ITP need some form of medical intervention. Data pooled from the evidence-based studies selected indicated that, on average, 64% of adult patients showed spontaneous remission following therapy, corticosteroids, or a splenectomy [25]. In 2006, another study was completed on 114 adults, and data collected showed that 30% of adult patients were in remission by six months, 53% between six months to three years, and 61% by five years following medical treatment in the form of corticosteroids or a splenectomy [26] This is a vast difference in interventions taken among children, as many can recover without medical treatment.

A study completed by the Intercontinental Childhood ITP Study Group looked at the rate of spontaneous remission in 1496 children diagnosed with ITP. Their data provided an estimate that 69% of the children in the sample were in complete remission by six months without extensive treatment [23]. The diagnosis process in children and adult ITP has changed as new evidence has presented against the need for extensive testing in most

patients. The American Society of Hematology has altered its recommendation against routine bone marrow examination as a diagnostic factor in children and adult ITP cases. Bone marrow extraction is now only recommended for adult patients over sixty, before a splenectomy, or in other circumstances, such as a negative response to treatment of continuous relapse [27]. This is due to the nature of the procedure, as it causes a significant amount of pain and discomfort for the patient with no guarantee of success. Children are not required to have a bone marrow aspiration at all unless there is persistent atypical findings on the peripheral smear. Initial treatment in children's ITP cases is now based on observational management techniques. This change is likely attributed to providers having a higher level of conformity when treating ITP and the low likelihood those children will develop spontaneous or extreme bleeding regardless of platelet count. Initial treatment is still the recommended course of action for adults with ITP as age, increased bleeding factors, and comorbid conditions are significant concerns for adult patients. While this is still the standard practice of care, recent studies have shown that there may be a benefit in utilizing observation techniques for low-risk adult patients [28].

### **The Difference in First-Line Children in Adults Compared to Children**

The initial first-line treatment is similar in both diagnosed adults and children. Typical treatment consists of corticosteroids, IV immunoglobins, and anti-D immunoglobulin. Recent studies have shown that the two groups' most significant difference in treatment is the initial therapy, as children are typically given IV immunoglobulin, and adults are prescribed corticosteroids [29]. In adults, prednisone, 1mg/kg orally, or high-dose dexamethasone 40 mg/day orally for four days, repeated every two to three weeks is the typical beginning of treatment. In a study looking at the long-term observation of 208 adults with chronic ITP, it has been reported that only 20% of patients that receive prednisone as their initial treatment maintain remission longer than six months [20]. Initial rates are between 70% and 80%, but relapse rates are higher in corticosteroids and low long-term remission rates [30]. More lasting outcomes have been reported with HDD as a sample of responders, resulted in having a 50% have a sustained response for up to two years [31]. Second-line treatments such as rituximab, an anti-CD20 monoclonal antibody that targets B sites, thrombopoietin receptor agents, and a splenectomy all had similar outcomes when comparing diagnosed adults and children. A recent study looking at the five-year outcome in diagnosed ITP patients following rituximab treatment showed that 38% of adults and 33% showed a sustained reaction after a year, and 26% of children and 21% sustained a response following five years [21]. An ongoing investigation into the symptoms, diagnostics, and treatment of diagnosed adults and children is needed to determine a clinical difference between the two groups. While it is apparent that there are distinct difference rates in the presentation of children and adult ITP patients, determinates into the biological background of the condition is a crucial point in understanding where the two groups differ. Studies looking at spontaneous remission rate, bleeding rate, comorbidity rate, chronicity rate, and genetics are

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all promising leads in determining the best diagnosis and treatment for diagnosed ITP patients.

### **The Treatment of Chronic ITP**

Due to the lack of understanding and the lack of long-term remission in chronic ITP cases, recent advances in new therapeutic techniques targeting multiple mechanisms are undergoing testing. A splenic tyrosine kinase inhibitor, fostamatinib, is an oral supplement approved by the U.S. Food and Drug Administration for chronic ITP patients who have either failed initial therapies or circumstances that cause the patient to receive recommended therapies. Fostamatinib inhibits a transduction signal that is essential to platelet phagocytosis, reducing antibody-dependent cellular phagocytosis [32]. Plasma cell targeting therapies have emerged as a target in removing anti-platelet antibodies once paired with anti B- cell therapies. A proteasome inhibitor, Bortezomib, is used to destroy anti-platelet antibodies and has been reported to reduce thrombocytopenia in select patients. However, the study has been halted due to the SARS-CoV-2 pandemic, and observations were seen in patients when the drug was used to treat myeloma [33]. Neonatal Fc receptor inhibitors bind IgG and transport the receptor through the placenta between the fetus and the mother. An open-labeled phase 2 trial is being conducted to determine whether the neonatal Fc receptor, rozanolixizumab, can be used as a treatment option for patients with chronic ITP. The study produced a report on sixty-six chronic patients indicating that 54.5%- 66.7% of patients reached a platelet level greater than  $50 \times 10^9/L$  after receiving a single dose through an infusion at 15 and 20 mg/kg. Researchers hope similar results will be reported as the study moves to phase 3 [34]. Inhibition of the complement pathway is another new therapeutic technique currently being studied for treating chronic ITP patients. The complement pathway begins with binding antibodies to glycoproteins, leading to platelet lysis by cytotoxicity and promoting phagocytosis of destructive cells by macrophages in the spleen [35]. While many treatments are available that help increase the platelet counts in individuals with chronic ITP, there is a lack of therapies available for individuals that experience inadequate responses.

### **Pregnancy and ITP**

Pregnancy is one factor that has been reported to cause several ITP cases. It has been shown that 10% of all pregnancies have complications due to thrombocytopenia. Out of all thrombocytopenic cases within the pregnancy, ITP, specifically, accounts for 5% of cases, meaning that one to two individuals per 1,000 pregnancies will be diagnosed. The disorder is usually diagnosed within the first or second trimester of pregnancy. The presentation of ITP is typically the same as in non-pregnant individuals, with the presentation of bruising, bleeding, and petechiae. ITP that began before pregnancy may remain dormant during gestation. A study that observed ninety-two women over one hundred and nineteen pregnancies throughout eleven years discovered that those previously diagnosed required less treatment for their ITP than those diagnosed not during pregnancy. The diagnosis of ITP during pregnancy requires a complete blood count, platelet count, and physical examination. An extensive peripheral

smear review is done to rule out pseudo thrombocytopenia, TTP, or preeclampsia, which may show increased fragmented red blood cells. Other factors such as hypertension, edema, or excessive weight gain could contribute to thrombocytopenia associated with a pregnancy-hypertensive disorder. All pregnant individuals with ITP should also be evaluated for the presence of HIV and HCV. Prior pregnancies and deliveries need to be considered to indicate whether there was extensive bleeding and whether the infant had thrombocytopenia or other complications during birth. In most cases, further testing for the underlying cause of ITP is usually delayed following birth to minimize harm to the mother and baby. Close communication with an obstetrician and hematologist is necessary for continuous monitoring. Many pregnant women with ITP are seen more often than those without, as visits consist on the schedule of monthly during the first trimester and second trimester, every two weeks after 28 weeks, and every week after 36 weeks. Most visits should be prioritized around monitoring blood pressure, weight, urine analysis, and platelet count checks. The need for intervention therapies varies on a case-by-case basis as well as consideration of bleeding; however, platelet counts must be considered significant if epidural anesthesia will be given during labor. More aggressive treatments are recommended closer to the time of birth to help increase the platelet count to a stable level deemed safe for the mother and baby. If platelets reach a level of  $10,000/\mu l$  during any point of the pregnancy, it is recommended that immediate treatment is initiated. During the second or third trimester or paired with bleeding, individuals with a platelet level of  $30,000/\mu l$  may need therapeutic therapies. The initial treatment for pregnant individuals with ITP consists of corticosteroids. The starting dose for most individuals is  $1mg/kg/day$  in the beginning, with a taper to occur after a few weeks [36]. This form of treatment is aided with caution, as corticosteroids have been reported to have unwanted side effects that are amplified during pregnancy. A few of the adverse effects include gestational diabetes, weight gain, osteoporosis, hypertension, and premature labor [37]. Other studies have linked the use of corticosteroids with the potential to cause facial deformities, such as an orofacial cleft in the newborn [38]. In situations where treatment is not needed urgently, physicians have recommended that a low dosage of prednisone is considered instead. A splenectomy is possible in the second trimester if a patient requires further treatment after failed attempts at less invasive therapies. The procedure is advised against before the second trimester as this can cause premature labor, and post-second trimester can cause an obstruction of view due to the enlarged uterus. In recorded patients who underwent splenectomy, 75% have achieved remission, as a laparoscopic approach is deemed safe for pregnant individuals. Depending on the severity of ITP progression, some alternations during delivery may be considered. The primary goal of managing the ITP is raising the platelet count to a safe level before a vaginal delivery and especially before a cesarean section to minimize the risk of neurological complications. The American Society of Hematology has reported that a platelet count of  $50,000/\mu l$  is sufficient for the mother and child during vaginal delivery and cesarean section. The British Society for Hematology has reported a higher number of platelets to be attained of  $80,000/\mu l$  due to the posed complications

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of a cesarean section and received of epidural anesthesia. The biggest concern of physicians regarding fetal thrombocytopenia is the risk of intracranial hemorrhage due to head trauma that can occur during the delivery of the fetus through the birth canal in vaginal delivery. However, this circumstance is extremely rare, with a reported incidence rate of 1%. If managed diligently and properly, neonatal thrombocytopenia is generally not associated with major morbidity. There is no preferred delivery method as no studies have indicated that cesarean section poses less of a risk for fetal intracranial hemorrhage or has helped increase the platelet counts within the mother. Pregnant patients with ITP should work closely with their obstetrician and hematologist to develop a plan that best suits their needs and the fetuses to ensure a safe delivery that poses a minimal risk [36].

### **The Effect of ITP on Quality of Life**

Living with ITP is a real challenge that many diagnosed patients face daily. The continuous platelet count checks, unwanted side effects, and anxiety surrounding the possibility of relapsing are all real challenges that individuals face. As this has become more of a prevalent issue among patients, researchers have begun to identify areas of health-related quality of life that are affected by ITP. Health-related quality of life (HRQoL) is a form of patient-report outcome (PROs) that is highly valued by the US Food and Drug Administration and the European Agency for the Evaluation of Medicinal Products for identifying measures that are significantly impacted by the disease or its treatment. Multiple studies have examined the testimonies of ITP patients and compiled a list of areas in that patients reported being directly affected. Commonly reported signs and symptoms include the inability to get out of bed, limitations of daily activities, bleeding, bruising, migraines, visual impairment, joint aches, and extreme fatigue. Direct statements were recorded for patients within the study, with one patient stating, "I am bruised all the time, and I am pretty used to it now. It is annoying, but it is just a way of life now." The commonly reported side effects of steroid-based therapy consist of mood swings, weight gain, anger, anxiety, and difficulty sleeping. Many patients commented on the extreme side effects of steroids, stating that they are "worse than chemo drugs" and now refuse to take them as "their quality of life means too much." Other treatment side effects, excluding steroids that were highly reported consist of headaches, hair loss, and susceptibility to bacterial and viral infections. One patient stated, "I am very susceptible to illness, colds, and lung problems. I have become fanatical with germs. I do not touch things." Many patients frequently mentioned feeling anxious and depressed due to the fear of their symptoms. Other patients stated that ITP had cast an emotional strain on their relationships as it has altered their personalities and permanently changed how they live their daily lives. A patient in one study looking at HRQoL in personal relations stated, "The thing about families is they look at you and expect to see you being strong; I feel like they expect me to be able to deal with this" [39]. Some patients reported being unable to participate in their daily activities because their ITP has caused them to have difficulty-sleeping, leading to extreme fatigue [41]. Some patients stated that their work was interrupted,

causing them to lose the ability to advance in their careers due to having to take time off or quit. One patient in the study stated, "I loved working, but the fact that I have to sleep when I am not working makes me want to work less so that I can do something besides sleep." Some patients have reported feeling extreme social embarrassment due to their side effects, especially bruising, as it felt like outsiders were looking at and judging their appearance. Many individuals stated that the bruising and bleeding that comes with ITP significantly impacted the health-related quality of life [39]. Lifestyle changes are very prevalent in individuals suffering from ITP. Dr. Claudia Tellez, a hematologist, and oncologist at Northwestern in Chicago, advises that all ITP patients take all activities at a slower pace and think about what sort of things can be taken in precaution to avoid the risk of creating a bleeding source. Sharper objects should be used with caution as even the smallest of cuts pose the risk of leading to an extreme bleeding episode. She tells all of her patients to be prepared for when a bleeding episode occurs, such as keeping extra bandages and gauze pads on hand in case the inevitable happens. Certain activities, especially high-impact exercise such as contact sports, are highly advised against. Trying to avoid injuries, especially head injuries, is crucial in maintaining the well-being of individuals with ITP as they have due to the elevated risk of bleeding and hemorrhages. Safer sports like swimming, stationary cycling, and yoga are better suited for patients with ITP. Aspirin and NSAIDs should be taken cautiously as they can interfere with the body's ability to clot and lead to a future risk of bleeding. Dr. Tellez suggests that consistently getting a good night's sleep with help ensure a high-functioning system, and individuals with ITP should aim towards nine hours of sleep each night for optimal health. Since fatigue is one of the significant complaints from individuals with ITP, sleep is a major factor in helping to ease the side effect of the symptom. Without proper sleep, the individual risks developing further unwanted symptoms or experiencing the impact of current symptoms more significantly. The US Department of Health has published guidelines that help individuals make better decisions when it comes to benefiting their health due to diet. While this diet is substantial for all individuals, patients with ITP need to keep up with their health intake to ensure a better quality of life. It is recommended that patients eat a variety of vegetables, especially starchy vegetables, beans, and peas. Whole fruits, whole grains, fat-free or low-fat dairy products, a variety of lean proteins such as seafood, and healthy oils. It is best to limit the intake of saturated fats, trans fats, added sugars, and high-sodium foods [41]. While patients with ITP may have to change their way of life, achieving a healthy, active, and fulfilling lifestyle with the proper precautions is possible.

### **Personal Account: Dr. Jennifer Shoenfelt**

ITP is a disorder that can significantly impact personal lives and relationships. ITP does not have the same effect on every individual, as it poses significant obstacles that must be overcome by the individual and their family and friends. Many individuals rely on others for help with their care, which can significantly strain relationships and personal lives. While it is currently not thought

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to be an inherited disorder, many diagnosed patients are concerned that there is a chance that the disorder could be passed on to future generations. While there is limited research on why ITP affects specific individuals within a family, providing adequate family history and genetics are two significant factors that are helpful for physicians in order to understand the condition and provide the proper diagnosis. Unfortunately, ITP is a disorder that has hit my family close to home. My aunt, Dr. Jennifer Shoenfelt, was diagnosed with ITP in 1978 at age fifteen and had been battling ITP for forty-four years. Her story began in high school when she first recalled discovering large bruises on both legs, which appeared suddenly over a couple of days. This prompted a visit to the pediatrician, where a CBC with differential was completed. Shoenfelt states, “this was my first CBC with differential and little did I know that this term would become one I use daily and come to understand all too well.” When the results had returned, and the physician discovered that she only had 13,000 platelets, Shoenfelt was quickly rushed to the Children’s Hospital and admitted to the hematology/oncology floor. She recalls feeling like she was on the floor where many children were dying, as many were frail and emaciated from the chemotherapy. Shoenfelt remembers that many of the other patient’s parents had disclosed that their child had very similar symptoms. When asked what the outcome of their cases was, Shoenfelt discovered that many of these patients were quickly diagnosed with leukemia shortly after presenting with similar symptoms. This evoked an extreme sense of panic, and questions filled her head as Shoenfelt recalls asking her new team if she would follow the same path and be diagnosed with cancer or even die. There were still no answers, and the initial testing gave physicians no lead into what was causing the dropping platelets; Shoenfelt’s doctor decided to conduct a bone marrow biopsy. Since ITP is a diagnosis of exclusion, a bone marrow biopsy is typically done on children to rule out the possibility of leukemia, myelodysplastic syndrome, or aplastic anemia once an abnormal smear has been presented. Before the biopsy, Shoenfelt’s physician mentioned the possibility of ITP as she recalled having a recent viral respiratory infection that could have triggered the disorder. Shoenfelt was also being treated for acne with a medication called tetracycline. Shoenfelt stated that the bone marrow biopsy was extremely painful and that it took the resident and attending physician multiple tries to complete the procedure successfully. The results indicated that Shoenfelt did not have leukemia and that her bone marrow was producing platelets. However, her body was somehow killing them off, which led to the diagnosis of ITP. Like in most childhood cases of ITP, no extreme measure is taken initially for treating ITP, and Shoenfelt was placed in the “watchful waiting category.” Shoenfelt was then observed until her platelet levels reached a safe level. At this time, the only available treatment was steroid therapy, and her physician did not feel as if her case was severe enough to resort to this option immediately. The other option was a blood transfusion, but the physician also decided against this treatment. After a couple of days, Shoenfelt’s platelet level rose to a level deemed safe “enough,” She was released from the hospital only to have to return daily for CBCs and platelet count testing. Over the next three years, Shoenfelt was monitored and would receive platelet count checks every

six months. She enrolled at The Ohio State University in 1981, and her physician deemed that her levels had reached a level for a certain period of time, putting her into the remission category. Shoenfelt’s life continued when she graduated college with a degree in physical therapy, got married, had children, and started her career in the workforce. It was not until 1996 that her symptoms suddenly returned, and she noticed small bruises and petechiae all over her body. As in the situation of when she was a child, a stat CBC was taken, and Shoenfelt was notified that her platelet level was 10,000, and she was taken to a hospital in Cleveland, Ohio. Shoenfelt was placed under the care of a new hematologist, where she was informed of the precautions that would need to be taken to ensure that there was no new risk of major bleeding. Like many ITP patients, Shoenfelt was warned of the dangers of driving, rough activities, and anything that could place her at risk of major bleeding, as she was informed to start taking her life very slowly. Due to the low level of platelets, Shoenfelt was treated with IV steroids and oral prednisone. At first, the steroid treatment was unsuccessful, and she needed several rounds of dosage increases and tapers. Her reaction to the steroids was similar to many ITP patients. Shoenfelt states, “steroids were a whole new experience for me; my face got a little puffy, my muscles were fatigued, and I got horrible infections.” She also remembers “having to lean against the kitchen sink to maintain balance, crying for no reason, having difficulty concentrating and forgetting what she was doing, and having no motivation.” This significantly impacted her daily life and activities and put a strain on her relationship and trying to be a good mother, causing Shoenfelt to withdraw from classes and work. At this time, Shoenfelt decided to begin studying for the MCAT while receiving treatments. It took a year for her platelet levels to reach a level deemed safe enough, and she was placed into remission again. During this period, Shoenfelt was accepted into medical school and began her first year in 1999, still in remission. While sitting in class, she noticed spots on her hands and wrist that worsened as the day went on. A stat CBC was taken, and the count revealed a new low of 5,000. Shoenfelt was immediately admitted and given a new hematologist. A transfusion was recommended, but Shoenfelt refused, and she now feels that “she was lucky to make it through.” Shoenfelt was then provided IV steroids, but this treatment was unsuccessful. A new treatment of WinRho, an anti-D agent, was given, and Shoenfelt recalls having a bad reaction where her body could not stop shaking. Once the reaction subsided, oral steroids were prescribed, and the side effects of constant weakness returned. Shoenfelt’s platelet levels once again reached a stable level, and she was put in remission again. During this time frame, she was able to graduate from medical school and begin her residency successfully. After completing her residency, Shoenfelt fell in love with psychiatry, where she decided to pursue her career. She has now been a practicing psychiatrist for almost fifteen years and is double board certified in child and adolescent adult psychiatry. Shoenfelt is still being treated for ITP and has been in remission for twenty-three years with occasional flare-ups of unexplained bruising and petechiae. Shoenfelt states she “watches closely and gets regular blood counts as needed.” She has faced adverse side effects from treatments as she has been diagnosed with osteoporosis, which her endocrinologist feels is directly related to steroid treatments.



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Over the years, she has had a few flare-ups that required a higher level of care. These treatments consisted of high-dose steroid bursts and IV I.G. but were unsuccessful. Currently, Shoenfelt is taking Promacta and receives weekly platelet counts, which have shown better results and have provided a solid stabilization of platelets. Shoenfelt continues to live a productive and busy life as she continues to work as a child and adolescent psychiatrist and is surrounded by her two children and three grandchildren, who bring her great joy. Although there is always a fear that ITP can return, maintaining a positive attitude and a healthy lifestyle makes it possible to live a relatively everyday life [42].

## Summary

Immune thrombocytopenic is an autoimmune blood disorder in which the body has fewer platelets circulating within the blood. The blood cannot clot appropriately as platelets' primary function is to seal the wound to maintain bleeding in case of an injury. When an individual has a low platelet count, there is a risk for excessive bleeding and bruising, as the body may have trouble stopping the bleeding. Individuals can experience different phases of ITP, as the diagnosis depends on severity and duration. However, ITP is a diagnostic exclusion disorder, meaning other problems must be ruled out before a patient is diagnosed. It is reported that ITP is caused by problems within the immune system, as this is the primary system that helps fight off infections and viral illnesses. In ITP, the body destroys the protection of these platelets, causing the body to lack the proper needs to fight off invaders. There has been no proven reason as to what causes the body to attack itself; however, researchers have determined that the risk of ITP is higher when taking certain antibiotics or antiviral medicines, after a bacterial or viral infection, or from certain vaccinations. ITP can occur in children and adults, with children having more likelihood of spontaneous remission. ITP in children typically affects both boys and girls at the same rate; however, in chronic ITP, females have a higher incidence rate than males. The most common type of ITP is Acute ITP, which often lasts less than six months as many individuals have a high chance of recovery without treatment. This form of ITP is seen more commonly in children. Chronic ITP is categorized as lasting more than six months to live and typically requires multiple treatments. Common symptoms in acute and chronic ITP include petechiae, purpura, nosebleeds, blood in the urine, and extreme tiredness. It is also possible that some individuals, especially children, may present with no or minimal symptoms. The diagnosis of ITP varies on a case-to-case basis, but a physician will typically gather information on the patient's medical and family history. A complete blood count will determine the number of platelets and blood cells within the body. A peripheral blood smear will be examined to determine the characteristics of the platelets. A bone marrow aspiration may be done if an individual has unwarranted findings on their peripheral smear or has shown no improvement after first-line therapy. For many individuals, ITP is not severe and can often go away independently. Children suffering from ITP will usually be observed before trying treatment as they have a high chance of spontaneous remission. Adults and chronic ITP patients have various types of treatments available

depending on the severity of the case. The first-line treatment in both children and adults is the use of corticosteroids. This form of medicine is used to increase the number of platelets; however, adverse side effects are possible if taken for too long. Second-line treatment includes TPO-Ras, platelet transfusions, and other medicines such as Rituximab and Romiplostim [9]. In severe cases or cases where all other treatments have failed, a splenectomy can be performed as the antibodies in the spleen destroy the platelets; however, this poses a significant infection risk to the individual. Currently, there is no best treatment for one individual as the treatment is highly dependent on platelet count and symptom presentation. Family history, current well-being, and genetics are all significant factors that a physician will consider to determine the best treatment for the patient. Most individuals with ITP can live a relatively everyday life with slight modifications to ensure no risk of significant bleeding, as the lower the platelet count, the greater the risk the individual faces. By working closely with a physician and ensuring that platelet counts are at a suitable level, it is possible to continue with all activities, as spontaneous remission is high in most patients, especially in children and acute ITP cases.

## Conclusion

Due to the uncertainty of ITP, the diagnosis and treatment is presumptive and vary significantly on the individual. ITP is suspected when an overall healthy person has a low platelet count or is discovered to have a lower level on a CBC. To diagnose ITP, the physician will look at medical history and do a physical exam with additional testing, including a CBC, peripheral blood smear, or bone marrow tests. ITP is typically caused by problems with the immune system, as usually, the immune system functions to help a person fight off infections and disease. In ITP, the immune system attacks the body's platelets, causing a decrease and limiting production. The reason the body has this reaction is unknown; by is suspected that certain medications, viral or bacterial infections, or vaccines can raise the risk of ITP. Almost all cases of individuals vary in presentation and severity. In acute ITP, extensive treatment is typically unnecessary as individuals have a high rate of spontaneous recovery. Chronic ITP can last for many years, and most suffering individuals can typically stop treatment at some point and maintain a safe platelet count. The treatment plan for an individual also is highly variable, and working closely with a physician, specifically a hematologist will ensure a safer level of care. In mild cases of ITP or no symptoms, no treatment may be needed, and the provider will continue to monitor the condition to ensure that the platelet level does not become too low. Medicines and procedures are available in chronic cases or cases with significant symptoms. Individuals typically begin with first-line treatments that are less invasive. The most prescribed first-line therapy consists of corticosteroids. More extensive treatment can range from other medication to spleen removal. Living with ITP is a challenge many diagnosed patients face, as symptoms and treatment plans can significantly affect their daily lifestyle. It has been reported that ITP has caused alterations in personal life, relationships, work status, and overall well-being. However, with the proper precautions, individuals can achieve a healthy and

satisfying lifestyle. Much more research is needed to understand the cause of ITP and how to best provide relief for suffering patients.

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