

Immune Thrombocytopenic Purpura in Children - A Review

Ponnumony John Solomon¹, Alen Chidambaram Priya Margaret^{2*}¹Professor & Director of Pediatrics, Sree Balaji Medical College & Hospital, Chromepet, Chennai, India²Assistant Professor of Pediatrics, Sree Balaji Medical College & Hospital, Chromepet, Chennai, IndiaDOI: [10.36347/sjams.2020.v08i03.050](https://doi.org/10.36347/sjams.2020.v08i03.050)

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*Corresponding author: Dr. Alen Chidambaram Priya Margaret DNB (Ped)

Abstract

Review Article

Immune Thrombocytopenic Purpura is one of the most common bleeding disorders of childhood. It presents with petechiae and bruising in a well looking child. It is caused by immune mediated destruction of platelets. Nowadays many centres in the world do not do bone marrow examination for diagnosis in typical cases of immune thrombocytopenic purpura. Majority of them get cured within 12 months, but about 20% of the cases continue to bruise/bleed on and off beyond 1 year also. Most children with ITP do not need treatment, but sometimes there will be need to treat because of the risk of life threatening bleeding. Steroids, IVIg, and Anti-D (Rh₀) immunoglobulin are standard first line treatments depending upon the situation. When the platelet count is very low there is a risk of intracranial bleed, and hence appropriate treatment should be given in such cases. The terminology and treatment protocols have changed since the time of its first report. Hence it is better to go for a review in this topic.

Key message: Children with immune thrombocytopenic purpura are not sick looking. Bone marrow examination is not done in many centres to diagnose Immune Thrombocytopenic Purpura. If the clinical picture is atypical BMA must be done. If the platelet count is very low there is a risk for intracranial bleed, and such cases should be treated promptly on time.

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INTRODUCTION

Immune Thrombocytopenic purpura is the most frequent hemorrhagic disease in children. In 1881 the Italian Pathologist Giulio Bizzozero described the fundamental role of platelets in hemostasis. In 1889 George Hayem established the relationship between purpura and thrombocytopenia [1]. Immune Thrombocytopenic Purpura (ITP) is an acquired bleeding condition characterized by the destruction of platelets caused by antiplatelet autoantibodies. The normal platelet count is between 1.5 lakh – 4.5 lakh /c.mm (150 – 450 x 10⁹ / L). ITP should only be diagnosed if the platelet count is repeatedly below 100 x 10⁹/L [6]. If thrombocytopenia is caused by the destruction of platelets by antiplatelet antibodies it is termed as Primary Immune Thrombocytopenic Purpura. In these cases there is a misdirected antibody response targeted against platelets, and as a result, the life span of platelets is shortened to a few hours (normal lifespan of platelets is 8-10 days). Auto-antibodies against platelet surface glycoproteins particularly anti-glycoprotein IIb/IIIa is usually detected in these patients. The destruction of platelets is very rapid, and the bone marrow is not able to produce platelets so fast to compensate the destroyed ones, and as a result the

platelet count drops and symptoms and signs of thrombocytopenia develop [2]. ITP should be diagnosed only if all the other causes of thrombocytopenia have been ruled out as it is a diagnosis of exclusion. In many patients with ITP there is a history suggestive of preceding viral infection.

The incidence of ITP in children and adolescents is 0.2 – 0.7 new cases per 10000 per year and the prevalence is 0.4 to 0.5 per 10000. The prevalence is significantly lower in children than in adults because the Pediatric ITP rarely becomes chronic [3, 6].

The terminology, classification and treatment have seen many changes over a period of 100 years. This condition was called as Idiopathic Thrombocytopenic Purpura. If these children recovered from the illness within 6 months it was called as acute ITP, and if there was no recovery within 6 months that was called as chronic ITP [4]. Now this understanding has changed. It is observed that upto 12 months children can develop complete remission and those cases who continue to have thrombocytopenia even after 12 months are diagnosed to have chronic ITP. Once it was thought that children with chronic ITP are unlikely to

remit. But now we know that about 50% of children with chronic ITP also achieve remission within four years of diagnosis [1].

An international working group of experts in this field met in Vicenza, Italy in October 2007 and gave a definition and recommendations on the various usages of terminology. They decided to avoid the term 'idiopathic' preferring 'immune' and to choose primary (as opposed to idiopathic) to indicate the absence of any obvious initiating and / or underlying cause. The term secondary immune thrombocytopenia has been proposed to include all forms of ITP except the primary ITP [9]. The term 'purpura' was felt inappropriate because bleeding symptoms are absent or minimal in a large proportion of cases. The acronym ITP now proposed to stand for Immune Thrombocytopenia was preserved because of its widespread and time honored use and taking into account its utility for literature searches [6, 9].

Immune Thrombocytopenic purpura is the most frequent hemorrhagic disease in Children [10]. Though ITP is thought to be a self-limiting disease in the majority of cases, it has tremendous social impact. The parents are all the time anxious that the child may bleed at any time particularly in the brain. Moreover the parents have to constantly supervise the child to avoid injuries. Children are upset because we advise them not to play casually according to their wishes (they should not participate in contact sports, etc).

Pathophysiology

Two major mechanisms contribute to the development of ITP: increased platelet destruction and insufficient platelet production [8]. Many ITP patients have antibodies directed to multiple platelet antigens. Platelet antigens recognized in ITP include membrane glycoproteins Ia/IIa, IIIa, Ib, IIb, and IX [2]. The T cell changes include excessive activation and proliferation of platelet antigen reactive cytotoxic T cells, production of abnormal helper-T cells, and abnormalities in the number and function of regulatory T cells. Platelet reactive CD4⁺ T cells have been found in the blood samples of ITP patients, with a major target antigen being GPIIb/IIIa [3].

The major physiological role of B - cells is antibody production. The number of circulating B cells secreting anti - GPIIb / IIIa antibodies have been reported to be increased in patients with ITP. The dysregulation of B cell development has also been associated with ITP. Serum concentrations of B cell activating factor were shown to be significantly increased in patients with active ITP. These findings support the treatment with Rituximab which produces B - cell depletion [3].

The spleen plays an important role in ITP. This is the primary site of antibody production. This is also the organ which clears antibody coated platelets. Human macrophages express several Fc receptors that bind IgG specifically. There are two types of Fc receptors, high affinity receptors and low affinity receptors. Removal of opsonised platelets is dependent on low affinity receptors [3, 4].

Based on these understandings the treatments have been planned in the following ways

1. Interference with antibody production.
2. Inhibition of Fc receptor-mediated opsonisation by splenic macrophages.
3. Immunosuppressant.
4. Stimulation of thrombopoiesis in the bone marrow [3].

Impaired function of megakaryocytes and an insufficient level of thrombopoietin (TPO) are two factors involved in decreased platelet production [8].

Diagnosis

The diagnosis of Immune Thrombocytopenic Purpura remains one of exclusion. Secondary forms of the disease occur in association with Systemic Lupus Erythematosus, the Antiphospholipid syndrome, Immunodeficiency states (IgA deficiency and common variable hypogammaglobulinemia), lymphoproliferative disorders (eg. Chronic Lymphocytic Leukemia), HIV and Hepatitis C virus infection, and therapy with drugs such as heparin and quinidine. In infants less than 3 months of age, passively acquired autoimmune or alloimmune thrombocytopenia must be excluded [7].

Clinical features

The typical presentation of ITP is that of a child who has been perfectly well and is now found to have developed unexplained bruises and petechiae on the skin in some or many parts of the body. Some of them remember an episode of brief viral illness a few weeks before this onset. The bruises may be mistaken and suspected to have been caused by non-accidental injury. These children may also have bleeding from mucus membranes like the gums, and also bleeds in the eyes and other areas in the body including intracranial bleeding which will present with head ache, convulsions and unconsciousness.

On examination the patient will be well looking and playful. There will be petechiae and echymosis. Typical petechiae are flat and not palpable. Any palpable purpura would become suggestive of a vasculitic purpura [6]. ITP per se increases the risk of infection. Platelets not only play a role in coagulation but also in the host defence against infections [6]. ITP patients will not present with Splenomegaly, Hepatomegaly or Lymphadenopathy. If the child is ill looking and has fever and organomegaly, then another serious illness should be thought off and investigated

appropriately. Systemic Lupus Erythematosus, Aplastic Anemia and Leukemia have other associated features, and if there is any doubt they should be investigated thoroughly.

Investigations

1. Complete Blood Count: In ITP cases Platelet count alone is low. White cells and Hemoglobin are usually normal. Peripheral smear study will confirm the reduction in the number of platelets, and the presence of normal white cells and red cells. If the patient has had significant bleeds and blood loss then there may be anemia. The mean platelet volume is normal or increased in ITP (more than 8 fL).
2. Blood Grouping: This is important because the patient may require transfusion. More over Rh typing is important to know if he is fit to receive Anti-D (Rh₀) immunoglobulin if required (It can be given to Rh+ patients only).
3. Coomb's Test: If this is positive autoimmune hemolytic anemia may be present and Evans Syndrome should be suspected. These patients cannot receive Anti-D (Rh₀) immunoglobulin because hemolysis will become worse.
4. Bone Marrow Examination: Many hematologists feel that Bone marrow examination is not a must for the diagnosis of ITP, and only in children with atypical findings they recommend Bone marrow examination. But in developing countries it is advisable to do Bone marrow examination due to several reasons. Particularly if there is a plan to start the patient on treatment with steroids, Bone marrow examination must be done and serious illnesses like Leukemia should be ruled out. In ITP the Bone Marrow study will be normal. In some cases there may be a slight increase in the number of Megakaryocytes which is a normal physiological response in ITP cases.
5. Antiplatelet antibodies: It is not important to do this investigation for newly diagnosed ITP cases but should be reserved for patients with persistent or chronic ITP and an atypical disease course[6]. Moreover it is not specific. It is expensive and not available in most of the places. It is useful only for research purpose.
6. Helicobacter Pylori Test: Since an association exists between this infection and ITP in some cases this investigation may also be done.
7. Specialized further testing for persistent or chronic ITP [6]. Antinuclear Antibody: Thrombocytopenia is found in some cases of SLE also. The detection of antinuclear antibodies (ANA), antiphospholipid antibodies, and lupus anticoagulant is also of prognostic relevance because thrombosis is more common in these patients[6].
8. Thyroid Function Tests: 10% of ITP patients have signs of thyroid autoimmune disease and may require therapy[8].

Differential Diagnosis

1. Drug induced thrombocytopenia. This is the most important differential diagnosis of ITP and can sometimes only be excluded by repeated history taking[6].
2. Fanconi's Anemia
3. Thrombocytopenia Absent Radius Syndrome (TAR)
4. Disseminated Intravascular Coagulation
5. Heparin Induced Thrombocytopenia
6. Systemic Lupus Erythematosus
7. HIV infection
8. Common Variable immunodeficiency
9. Lymphoma
10. Autoimmune Lymphoproliferative syndrome
11. Wiskott - Aldrich syndrome
12. Evans Syndrome
13. Von Willebrand Disease type 2b
14. Large Hemangiomas (Kasabach-Merritt syndrome)
15. Severe Vitamin deficiencies e.g. B12, Folic acid.
16. EDTA Pseudothrombocytopenia

A good history and meticulous clinical examination will rule out the above conditions. Fanconi's Anemia and TAR syndrome may be associated with congenital external anomalies. Wiskott - Aldrich syndrome is an x-linked recessive disorder, and the patients are males and they have thrombocytopenia with small platelets, eczema and recurrent infections. To diagnose SLE, among the 11 clinical criteria, and 6 immunologic criteria at least 4 criteria must be positively present.

Treatment

Treatment is not recommended for newly diagnosed ITP in children and adolescents with no or only mild bleeding [6]. Most of the patients with ITP have mild symptoms only, and in the majority of them the disease is self-limiting. Hence these patients do not need any significant treatment. Reassurance, education and counseling of the parents regarding care and nature of illness are important. At the same platelet count the chances of bleeding in ITP is less than in marrow failure syndromes [4]. But most of the time it is difficult to convince some parents. They will move from one doctor to the other and finally land up in total confusion and chaos. Some are not willing to wait and see the course to face it boldly. Restricting the activities of children and preventing injuries may be a tough job for parents. In such patients it is better to start on any one of the drugs which is standard with fewer side effects. If the platelet count is less than 10000 / μ L or if there is active clinical bleeding (e.g. Gum bleeds, epistaxis, etc) it is advisable to give drug treatment. If there is a significant risk of intracranial bleed then we should administer IVIg or Anti D (Rh₀) immunoglobulin or High dose steroids along with platelet concentrate. If there is little or no treatment response, the diagnosis should be questioned. The mortality from intracranial

hemorrhage was reported to be 57% in 1994, but in later series it was reported as 20-25% [5].

Anti-platelet antibodies bind to the transfused platelets also and these platelets get destroyed in a few hours. Hence platelet transfusion is usually not recommended unless there is life threatening bleeding.

The front line treatment is given below.

American Society of Hematology recommends the use of a single dose of Intravenous immunoglobulin IVIg (0.8-1.0g/kg) over 4-6 hours or a short course of corticosteroids as the first-line treatment. The platelet count will rise within 48 hours. IVIg can be given for 2 days also, but it is expensive. The administration of this drug may be followed by headache and vomiting in some cases. When the expertise of a well-qualified hematologist is not available it is better to use IVIg. It may allay the anxiety of the practitioner from partially treating a case of Acute Lymphoblastic Leukemia in this situation. A good response to this treatment with IVIg may also confirm the diagnosis of ITP. The response may last for more than 3 weeks. IVIg down regulates Fc-mediated phagocytosis of antibody coated platelets.

Prednisolone in a dose of 1- 4 mg/kg/24 hour induces a rise in platelet count but the rise is slower than with IVIg. It is usually given for 1-2 weeks and then tapered [4]. Dexamethasone may also be given. If high doses of steroids are given for a prolonged period, there is risk of hypertension, cushingoid features, diabetes mellitus, cataract, osteoporosis, mood disturbances etc. If steroids are used chronically, then efforts should be made to find the lowest therapeutic dose to minimize toxicity. The mechanism of action of the drug is immunosuppression, interference with antibody production, impairment of antibody coated platelet clearance by macrophages, and impairment of splenic function. The duration of corticosteroid therapy should not be too short (not less than 3 weeks) [6].

Anti-D (Rh₀) immunoglobulin is a good option as it increases the platelet count in 48-72 hours. This is prepared from plasma taken from rhesus-negative donors who have been immunized against the anti-D-antigen. This can be given only if the patient is Rh positive. It is contraindicated in Rh negative patients, Evans syndrome and splenectomised patients. The dose recommended is 50-75 µg/kg I.V over 30 minutes. The patient should be followed up for 8 hours after the infusion because rarely it may produce life threatening intravascular hemolysis. The mechanism of action of this drug is induction of subclinical immune mediated hemolytic anemia and Fc receptor competition, and Fc receptor down regulation on reticuloendothelial cells. The effect of the drug will last for about 3 weeks. In life threatening bleeding if the above measures do not achieve hemostasis consider administration of rituximab and thrombopoietin receptor agonists (TRAS).

The second – line approaches are given below.

Rituximab (Anti-CD20 antibodies) is administered in a dose of 375 mg/m² weekly once for 4 consecutive weeks. It is a monoclonal antibody which causes lysis of B lymphocytes. It eradicates the plasma cell clone making antiplatelet antibody. The response to treatment is often delayed for weeks to months, but the response may last for 6-12 months and hence it will be useful in chronic ITP cases. Infusion related side effects including cytokine release syndrome are reported commonly after the first infusion. They include fever, chills, nausea, vomiting, allergic reactions like rash, pruritus, angioedema, bronchospasm and dyspnoea, and flushing. Rituximab can produce impaired humoral responses to vaccination. Hence it is better to vaccinate children before treatment if possible, particularly if splenectomy is contemplated in the near future. This drug is very expensive.

Other drugs that have been tried are immunosuppressive agents such as azathioprine, tacrolimus, sirolimus, cyclosporine etc, thrombopoietin receptor agonists like eltrombopag, romiplostim etc, Anti- CD 40 ligand monoclonal antibody, IDEC-131 humanised monoclonal antibody, chemotherapeutic agents like cyclophosphamide, mercaptopurine, vincristine, and recombinant activated Factor VII (rFVIIa), Hydroxychloroquin, and Mycophenolate Mofetil etc.

Splenectomy should be considered as the last resort if there is no other alternative. It produces a quick response, but some patients may still relapse after a few months or years. Splenectomy should be postponed atleast up to 5 years of age, and before that vaccination for Neisseria, Hemophilus and Pneumococcus should be completed because of the high incidence of post splenectomy sepsis. Following splenectomy patients should be on penicillin prophylaxis lifelong [2]. For multirefractory ITP, combination therapy with rituximab plus steroids plus TRAs may be tried. For mild oral mucosal hemorrhages, menorrhagia and dental procedures, we can give antifibrinolytic tranexamic acid.

Important points for parents of children with ITP to remember

1. Intramuscular injections should be avoided. Vaccines that are usually given intramuscularly can be given subcutaneously in these children. ITP patients should receive all standard vaccinations. Live attenuated vaccines are contraindicated for ITP patients with immunosuppressive treatments with corticosteroids; rituximab etc. IVIGs can also affect the efficacy of live vaccines. There should be an interval of atleast 3 months after IVIGs.
2. Aspirin and nonsteroidal anti-inflammatory drugs should be avoided. Pain and fever can be managed with paracetamol.

3. Avoid injuries as far as possible. Contact sports like Boxing, Football, Hockey, Kickboxing, Martial arts, Karate, Rugby, Wrestling, etc. must be avoided.
4. When the platelet count is below 75000/ μ L the patient should be advised against any activity which is associated with a significant risk of trauma.
5. Prevent constipation. If the patient has constipation or severe cough it should be treated promptly to prevent intracranial bleed when the platelet count is very low.
6. Patient should be under the care of a good Pediatric Hematologist.
7. If any surgery is necessary it should be done in a well-established centre where there is facility and expertise available for the treatment of such bleeding disorders.

CONCLUSIONS

Immune thrombocytopenic Purpura is a common hematologic disorder of childhood. It is caused by an autoimmune process characterized by the inappropriate production of antibodies directed against normal platelets and megakaryocytes. Antibody coated platelets are destroyed in the spleen and hence the number of circulating platelets is reduced. Most of the cases of ITP are self-limiting and they do not need any specific treatment. But often situations will compel the practitioner to give treatment. The medication to be given depends upon the circumstances. If it is an emergency, drugs like IVIg, or Anti-D (Rh₀) immunoglobulin, or high dose steroid should be administered in addition to platelet transfusions. In other situations low dose oral steroids can be given for a short period if need be. Patient should be under the care and advice of a good Pediatric Hematologist.

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