Pediatric Immune Thrombocytopenia

Immune Thrombocytopenia (ITP) is a rare, acquired autoimmune disorder characterized by lower than normal platelet counts (< 100 x 10^9/L). The immune destruction of platelets may result in an increased risk of bleeding and put patients at risk for serious bleeding complications. ITP may be categorized as primary or secondary based on how the disease is identified.[1,2]

Epidemiology in Pediatric Patients

80% of ITP Patients Are Diagnosed with Primary ITP[1-3]

Primary ITP is a result of the absence of a diagnosis from other causes of thrombocytopenia

Primary ITP is a distinct disease from secondary ITP

Secondary ITP[1-3]

Thrombocytopenia associated with underlying disorders such as HIV, autoimmune diseases, *H. pylori*, or immune dysregulation

In 60% of pediatric patients, ITP may follow an acute infection (viral or other) within the previous 2 months; other immunogenic events such as allergic reaction, measles mumps rubella (MMR) vaccination, or insect bites have been reported to precede ITP presentation[4-5]

Incidence of acute ITP† in children: 1.9-6.4 per 100,000 person-years[5-6]

Incidence peaks between 2-6 years of age

Phases of ITP[1,2,7,8]

Based on time from diagnosis

DIAGNOSIS

Newly Diagnosed < 3 months

Persistent* 3-12 months

~70-80% may spontaneously resolve within 6 to 12 months

Chronic > 12 months

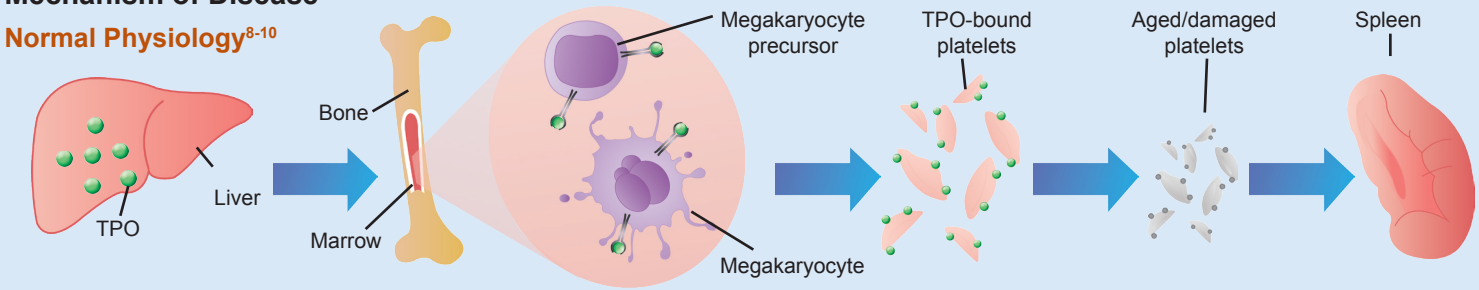
~20-30% develop persistent or chronic ITP

*Includes patients not reaching spontaneous remission or not maintaining complete response to therapy.

†Acute ITP in young children is defined as having a very sudden onset and the symptoms usually disappearing in less than 6 months.

Mechanism of Disease

Normal Physiology[8-10]



Thrombopoietin (TPO) is produced by the liver and is the cytokine responsible for megakaryocyte development and platelet production

TPO binds via the TPO receptor to stimulate the differentiation of megakaryocytes into platelets

Serum TPO levels are inversely proportional to platelet counts

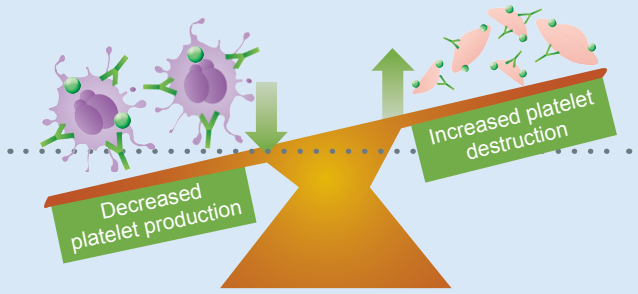
Platelets persist in circulation for 8-10 days before they are cleared by the spleen

ITP Pathophysiology[8,11]

Autoimmune responses affect the rate of platelet production and platelet turnover.

Normal rate of platelet production and turnover

Increased megakaryocyte dysfunction and reduced TPO stimulation leads to fewer platelets[12-15]



Antibody-bound platelets and TPO are rapidly removed by the spleen[12,17]

Desialylated platelets are removed in the liver[17,19]

Platelets are recognized by cytotoxic T cells and undergo cell death[18]

Antibody-mediated damage and T cell-mediated dysfunction of megakaryocytes impair platelet production[12-15]

Antibody-mediated and cytotoxic T cell-mediated increase in platelet destruction[12,16-18]

Diagnosis

Primary ITP Remains a Diagnosis of Exclusion[1]

No robust clinical or laboratory parameters are yet available to establish a diagnosis.

Diagnosis is usually made based on the patient's medical history, physical examination, complete blood count, and examination of a peripheral blood smear.

Secondary ITP should be excluded by checking for causes of thrombocytopenia known to lead to secondary ITP.

Signs and Symptoms[7]

- Petechiae or purpura
- Persistent bleeding symptoms from cuts/ other injuries
- Mucosal bleeding
- Frequent/heavy nose bleeds
- Hemorrhage from any site

Burden of Disease

Although ITP in pediatric patients is more likely to be acute and spontaneously resolve, pediatric patients may still struggle with having a high clinical burden of disease during the course of the disease that can significantly impact their lives[19]

In pediatric patients, ITP is associated with

Higher risk of bleeding events[20]

91% of patients with ITP have reported a bleeding-related event. Less than 1% of ITP patients have reported an intracranial hemorrhage from a bleeding-related event.

Increased use of rescue medications[4,7]

Corticosteroids or immunoglobulins

Higher costs associated with increased hospitalization[21]

Mean hospitalization cost per event was $5,398 for pediatric ITP discharges vs. $1,964 for non-ITP pediatric discharges

ITP affects both pediatric patients and their caregivers[19,22,23]

- Concern for bleeding (gastrointestinal bleeds, intracranial hemorrhage, hematuria)
- Uncertain clinical course
- Fatigue
- Interruptions to daily routines
- Concern for hospitalization
- Dietary restrictions and/or medication side effects

Managing Pediatric Patients with ITP[1,7,8]

Primary goal: sustain platelet counts for adequate hemostasis and reduce bleeding risks

Watch and Wait (platelet counts > 20 x 10^9/L)	No or mild bleeding (skin manifestations only - e.g., bruising/petechiae), regardless of platelet count Strategy is to choose to live with child's current platelet counts while carefully monitoring the disease

Treatment strategies

Inhibition of Fc receptor-mediated opsonization by splenic macrophages	Immuno-suppression	Stimulation of thrombopoiesis in the marrow	Interference with antibody production

1st line therapy

Corticosteroids: Increase platelet levels by preventing destruction of platelets by macrophages in spleen and liver

Immunoglobulins: Provides antibody excess and Fc receptor competition with Fc receptor downregulation on reticuloendothelial cells

2nd line therapy

Thrombopoietin-receptor agonist (TPO-RA): Mimic body's endogenous thrombopoietin to stimulate platelet production in bone marrow

CD20-targeted monoclonal antibodies: Depletes CD20+ B cells, decreasing production of antiplatelet autoantibodies and blocking macrophage action

Immunosuppressant: Inhibits T cells to interfere with immune activation

Splenectomy: Surgical removal of the organ responsible for the majority of clearance of antibody-bound platelets. Recommended to wait at least 12 months from diagnosis in case of spontaneous remission

Guideline recommendations (ASH and ICR)[1,7]

Immunoglobulins or a short course of corticosteroids are recommended as initial treatment

Due to the relatively high rate of spontaneous remission of pediatric ITP, high risk of post-splenectomy and lifetime sepsis, and availability of other treatment options, splenectomy is generally deferred

ASH = American Society of Hematology; ICR = International Consensus Report.

References:
1. Neunert C, et al. *Blood*. 2011;117:4190-4207. 2. Rodeghiero F, et al. *Blood*. 2009;113:2386-2393. 3. Cines DB, et al. *Blood*. 2009;113:6511-6521. 4. Labarque V, et al. *Eur J Pediatr*. 2014;173:163-172. 5. Yong M, et al. *Br J Haematol*. 2010;149:855-864. 6. Terrell DR, et al. *Am J Hematol*. 2010;85:174-180. 7. Provan D, et al. *Blood*. 2010;115:168-186. 8. D'Orazio JA, et al. *J Pediatr Hematol Oncol*. 2013;35:1-13. 9. Deutsch VR, et al. *Br J Haematol*. 2006;134:453-466. 10. Kaushansky K. *J Clin Invest*. 2005;115:3339-3347. 11. Lambert MP, et al. *Blood*. 2017;129:2829-2835. 12. Houwerzijl EJ, et al. *Blood*. 2004;103:500-506. 13. Kuter DJ, et al. *Hematol Oncol Clin North Am*. 2009;23:1193-1211. 14. McMillan R, et al. *Blood*. 2004;103:1364-1369. 15. Gernsheimer T. *Oncologist*. 2009;14:12-21. 16. Li J, et al. *Nat Commun*. 2015;6:7737. 17. Kile BT. *Nat Med*. 2015;21:11-12. 18. Olsson B, et al. *Nat Med*. 2003;9:1123-1124. 19. Heitink-Polle KM, et al. *Haematologica*. 2014;99:1525-1531. 20. Kuhne T, et al. *Haematologica*. 2011;96:1831-1837. 21. Tarantino MD, et al. *Platelets*. 2016;27:472-478. 22. Klaassen RJ, et al. *J Pediatr*. 2007;150:510-515,515.e1. 23. Giordano P, et al. *Pediatr Hematol Oncol*. 2014;31:534-547.