Immune Thrombocytopenia (ITP)

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 puts patients at risk for serious complications. ITP may be categorized as primary or secondary based on how the disease is identified.[1,2]

Etiology and Diagnosis[1-3]

80% of ITP patients are diagnosed with Primary ITP

Primary ITP

Primary ITP is defined as platelet count < 100 x 10^9/L in the absence of other potential causes of thrombocytopenia. Normal platelet counts range from 150-400 x 10^9/L.

Secondary ITP

Occurs in association with other underlying disorders such as autoimmune diseases, chronic lymphocytic leukemia, and infections (Hep C, HIV, *H. pylori*).

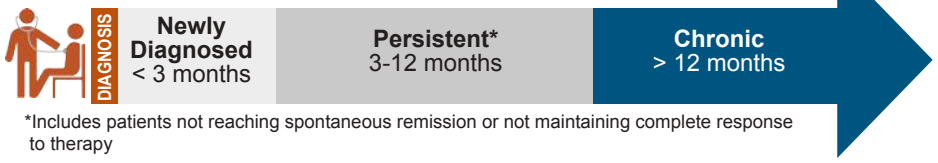
Diagnosis is generally based on the patient's history, physical examination, labs (complete blood count), and examination of a peripheral blood smear. However, ITP remains a diagnosis of exclusion, as no robust clinical or laboratory parameters are yet available to establish a diagnosis.[1,3]

Signs and Symptoms[4]

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

Phases of ITP[1,2]

Based on time from diagnosis



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

Epidemiology

ITP is a rare disease that can affect both adults and children[4]

In adults, ITP occurs more frequently later in life and rarely resolves without treatment[5-7]

55-60 years old

Median age at diagnosis is between 55 and 60 years[6,8]

2.9-3.9

per 100,000 person-years

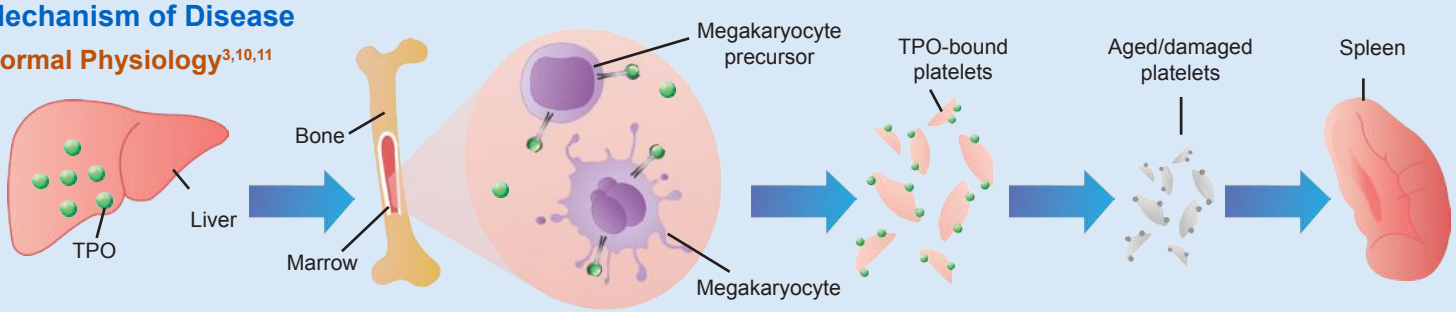
Incidence of adult ITP[5-7]

In patients < 60 years old, ITP occurs more frequently in females[5-7]

Natural history studies in ITP suggest that ~10% of newly diagnosed cases will spontaneously resolve within 6 months[9]

Mechanism of Disease

Normal Physiology[3,10,11]



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

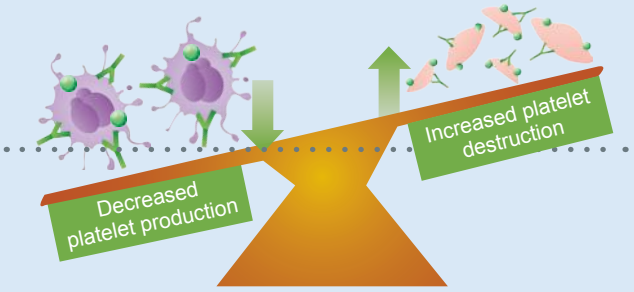
Platelets persist in circulation for 8-10 days before they are cleared by the spleen

ITP Pathophysiology[11,12]

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[13-15]



Antibody-bound platelets and TPO are rapidly removed by the spleen[14,17]

Desialylated platelets are removed in the liver[17,18]

Platelets are recognized by cytotoxic T cells and undergo cell death[19]

Antibody-mediated damage and T cell-mediated dysfunction of megakaryocytes impair platelet production[13-16]

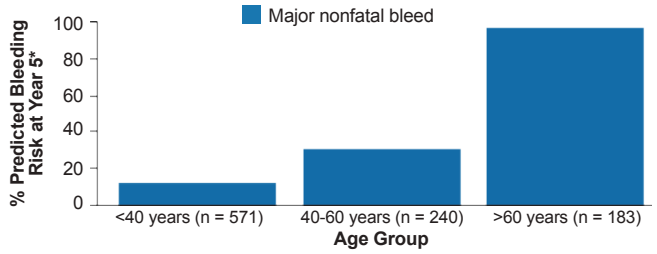
Antibody-mediated and cytotoxic T cell-mediated increase in platelet destruction[13,17-19]

Clinical Burden of Disease

Increased morbidity in patients with ITP, compared to non-ITP patients, primarily driven by a high risk of bleeding related events and hospitalizations[8,20]

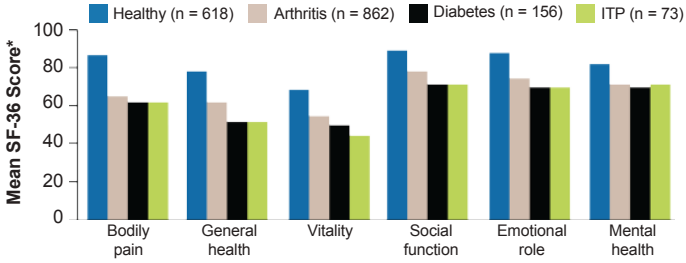
1-2% of patients with ITP develop intracranial hemorrhage[8,21]

A majority of adult ITP patients will experience at least one significant bleeding event, with higher risks in elderly patients (> 60 years)[22]



*Model developed from pooled analysis of ITP patients with persistently low platelet counts

ITP has an impact on patients' lives, similar to or worse than that of other chronic conditions[20]



*All scores range from 0-100; higher scores indicate better health-related QoL

Treatment of Adult ITP

Goals of treatment[1,2]:

Sustain platelet counts that are associated with adequate hemostasis, and reduce bleeding risk with minimal side effects

Assessing for treatment includes several factors[1,2]:

- Severity and extent of bleeding
- Activity and lifestyle
- Patient preference
- Risk factors for bleeding (e.g., previous bleeding episodes)
- Current medications that may increase risk of bleeding

Treatment strategies[1,2,4,11]:

Suboptimal Platelet Production	Increased Platelet Destruction
Reduced TPO production results in decreased platelet production	Immune dysregulation results in antibody-mediated megakaryocyte damage and dysfunction
	Immune dysregulation results in platelet destruction
Increase TPO levels	**Decrease immune response**
Thrombopoietin-receptor agonist (TPO-RA): Mimic body's endogenous thrombopoietin to stimulate platelet production in bone marrow	**Corticosteroids:** Increase platelet levels by preventing destruction of platelets by macrophages in spleen and liver **CD20 targeted monoclonal antibodies:** Depletes CD20+ B cells, decreasing the production of antiplatelet autoantibodies and blocking macrophage action
	Immunoglobulins: Desensitize immune system **Immunosuppression (azathioprine, cyclosporin):** Nonspecifically inhibits T cells to interfere with immune activation **Splenectomy:** Removing the spleen decreases platelet destruction

The ICR and ASH provide recommendations for assessing response to ITP treatments[1,2]

Complete Response (CR)	Response (R)	No Response (NR)
A platelet count ≥ 100 x 10^9/L measured on 2 occasions > 7 days apart and the absence of bleeding.	A platelet count ≥ 30 x 10^9/L and a greater than 2-fold increase in platelet count from baseline measured on 2 occasions > 7 days apart and absence of bleeding.	A platelet count < 30 x 10^9/L or less than 2-fold increase in platelet count from baseline or in the presence of bleeding. Platelet count must be measured on 2 occasions more than a day apart.

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. Kaushansky K. *J Clin Invest*. 2005;115:3339-3347. 4. Provan D, et al. *Blood*. 2010;115:168-186. 5. Schoonen WM, et al. *Br J Haematol*. 2009;145:235-244. 6. Frederiksen H, et al. *Blood*. 1999;94:909-913. 7. Moulis G, et al. *Blood*. 2014;124:3308-3315. 8. Altomare I, et al. *Clin Epidemiol*. 2016;8:231-239. 9. Stasi R, et al. *Am J Med*. 1995;98:436-442. 10. Deutsch VR, et al. *Br J Haematol*. 2006;134:453-466. 11. D'Orazio JA, et al. *J Pediatr Hematol Oncol*. 2013;35:1-11. 12. Lambert MP, et al. *Blood*. 2017;129:2829-2835. 13. Houwerzijl EJ, et al. *Blood*. 2004;103:500-506. 14. Kuter DJ, et al. *Hematol Oncol Clin North Am*. 2009;23:1193-1211. 15. McMillan R, et al. *Blood*. 2004;103:1364-1369. 19. 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. 20. McMillan R, et al. *Am J Hematol*. 2008;83:150-154. 21. Neunert C, et al. *J Thromb Haemost*. 2015;13:457-464. 22. Cohen YC, et al. *Arch Intern Med*. 2000;160:1630-1638.