BMJ Best Practice

Immune thrombocytopenia

Straight to the point of care

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Summary

Immune thrombocytopenia (ITP) in children typically presents with a preceding viral illness and an abrupt onset. There is a female preponderance among adults, who may present with thrombocytopenia with or without bleeding.

Petechiae occur primarily on the lower limbs, but can appear anywhere on the body (including mucosal membranes), particularly if thrombocytopenia is severe. Bruising is common. Mucosal bleeding may also occur in more severe cases. Intracranial bleeding is reported in approximately 0.5% of children and 1.5% of adults.

Complete blood count and peripheral blood smear show isolated thrombocytopenia.

Treatment is based on platelet count and bleeding symptoms. Patients with life-threatening bleeding, regardless of platelet count, can be considered for combination therapy with corticosteroids, intravenous immune globulin (IVIG), and platelet transfusion.

Initial treatment options for newly diagnosed ITP include observation, or a corticosteroid and/or IVIG depending on platelet count and bleeding symptoms. Intravenous Rho(D) immune globulin can be considered in patients who are rhesus-positive and nonsplenectomized.

Subsequent treatment with thrombopoietin receptor agonists, rituximab, or fostamatinib (adults only) can be considered in patients who are unresponsive to, or intolerant of, initial treatment. Splenectomy may also be an option from 12 months after diagnosis.

Salvage therapy with oral immunosuppressants, such as mycophenolate, azathioprine, or dapsone, can be considered in patients who do not respond to multiple subsequent treatments.

Prognosis is good in children, with up to 80% achieving a spontaneous remission. Mortality is higher in older patients and in those unresponsive to several lines of treatment.

Definition

Primary ITP, also known as immune thrombocytopenic purpura, is a hematologic disorder characterized by isolated thrombocytopenia (platelet count <100 × 10^3/microliter) in the absence of an identifiable cause.[1] The thrombocytopenia is secondary to an autoimmune phenomenon and involves antibody destruction of peripheral platelets.[2]

Secondary ITP includes all forms of ITP where associated medical conditions or precipitants can be identified. The distinction between primary and secondary ITP is clinically relevant because of their different natural histories and distinct treatments, including the need to treat the underlying condition in secondary ITP.[3] The focus of this topic is primary ITP.

THEORY

Epidemiology

In Europe, adult immune thrombocytopenia (ITP) has an incidence of 1.6 to 3.9 cases in 100,000 per year.[4] Incidence increases with older age and there is a higher female-to-male ratio (3:1) in younger patients. A nationwide population study in the UK reported a crude incidence of 3.9 cases in 100,000 person-years, with a higher incidence in women.[5] A nationwide population study in France reported an incidence of 2.9 cases (of ITP necessitating health care) in 100,000 per year.[6] ITP was secondary to other disease in 18% of cases.[6] Childhood ITP has an incidence of between 1.9 and 6.4 in 100,000 per year with equal distribution between the sexes, and tends to result in spontaneous remission.[4]

Data on epidemiology from the US and other countries is lacking. One study of two US private healthcare claims databases from 2012 to 2015 estimated an annual incidence of 6.1 cases per 100,000 population. Incidence was higher for women (6.7 per 100,000) than for men (5.5 per 100,000), and highest in children ages 0-4 years (6.1 per 100,000) and adults ages ≥65 years (13.7 per 100,000).[7] The prevalence of ITP has been estimated as between 9.6 and 20.0 in 100,000 in the US, based on insurance administrative data, with higher prevalence with increasing age and among female adults.[8] [9]

Etiology

The etiology responsible for breaking immune tolerance and for initiating the autoimmune attack against platelets remains unknown. Genetic influences and immune dysregulation, mainly through autoreactive T-cell abnormalities and environmental triggers, may contribute to the progression of the disease.

Pathophysiology

The pathophysiological process leading to thrombocytopenia in immune thrombocytopenia (ITP) is complex and is still being investigated, but current evidence suggests that it involves several different processes including increased destruction of platelets in the spleen by antiplatelet antibodies (mainly directed against GPIIb-IIIa), impairment/inhibition of platelet production due to suppression of normal megakaryocyte development by autoantibodies, and T cell-mediated destruction of platelet and megakaryocyte in the bone marrow.[10] [11] These processes may be appropriate targets for treatment.[12]

Classification

Types of immune thrombocytopenia (ITP)

1. Primary ITP

2. Secondary ITP

- HIV
- Hepatitis C
- *Helicobacter pylori*
- Immunodeficiencies
- Immunologic/autoimmune disorders (e.g., systemic lupus erythematosus, Evans syndrome, antiphospholipid syndrome, and autoimmune thyroid disease)
- Lymphoproliferative disorders

- Drug-induced
- Vaccine exposure (very rare).

Case history

Case history #1

A 50-year-old woman presents approximately 3 weeks after an upper respiratory tract illness with petechiae, easy bruising, and gum bleeding. She has no personal or family history of a bleeding disorder and takes no medications. Physical exam is normal except for petechiae and bruising. Specifically, she has no lymphadenopathy or hepatosplenomegaly. Complete blood count reveals thrombocytopenia with a platelet count of 12 × 10^3/microliter but other cell lines are within normal limits. Peripheral blood smear shows thrombocytopenia but no other abnormalities.

Other presentations

In about half of adult cases, thrombocytopenia may be an incidental finding on routine complete blood count or during investigation for another illness. Patients may have no bleeding symptoms or signs.

Rarely, patients can present with organ- or life-threatening major bleeds and require emergency treatment.

Children typically present with sudden onset of mucocutaneous bleeding with extensive bruising and petechiae.

Approach

Immune thrombocytopenia (ITP) is a diagnosis of exclusion; history, exam, and tests are directed at ruling out other potential causes of a low platelet count.

History

Patients may present with bleeding (e.g., bruising, petechiae, hemorrhagic bullae, bleeding gum). Fatigue is also commonly reported, and there may be a preceding viral illness (particularly in children), but otherwise the patient usually feels well. Some patients present with no signs or symptoms. In about half of adult cases, thrombocytopenia is an incidental finding on routine complete blood count (CBC) or during investigation for another illness.

History should include differential diagnoses of thrombocytopenia and secondary causes of ITP. A full medication history (including herbal remedies) should be carried out to identify potential causative agents for thrombocytopenia.

There are no known risk factors for ITP apart from a higher prevalence in women of childbearing age, and in males and females younger than 5 years and older than 65 years.[6] [8] [9] The coexistence of other factors or diseases prompts the diagnosis of secondary ITP.[15]

Exam

Physical exam is often normal except for possible bruising, petechiae, or bleeding related to thrombocytopenia. Specifically, there should be no lymphadenopathy or hepatosplenomegaly. A standardized bleeding assessment tool can be used to evaluate the bleeding symptoms of ITP and to score its severity.[15] [16]

Investigations

CBC and peripheral blood smear:

- CBC reveals isolated thrombocytopenia (platelet count <100 × 10^3/microliter) without other abnormalities. There should be no evidence of myelodysplasia or other disorders (i.e., Pelger-Huet anomaly, nucleated red blood cell, schistocytes, immature granulocytes, large granular lymphocytes). Other cell lines (i.e., red cells and white cells) should be normal.
- Peripheral blood smear distinguishes between true thrombocytopenia and pseudothrombocytopenia (a spuriously low platelet count in blood samples collected into ethylenediaminetetraacetate [EDTA]-containing collection tubes; occurs in about 0.1% of adults); this can be uncovered by a normal platelet count on peripheral blood smear or by using a citrate tube instead of an EDTA tube.

Bone marrow biopsy and/or aspirate (with flow cytometry and cytogenetic testing):

- Only considered if atypical blood film features are present. Not routinely recommended at initial diagnosis, but it may be considered in patients who are unresponsive to medical therapy, or prior to splenectomy.[15]

Exclusion of secondary causes

Exclusion of the many secondary ITPs is of critical importance, because most of these forms have a different natural history and require different management (e.g., treatment of underlying disease, such

as systemic lupus erythematosus, or antiretroviral therapy for newly diagnosed HIV disease; acute management of ITP may also be required if acute thrombocytopenia or bleeding symptoms/signs are present).

Routine testing for HIV and hepatitis C infection is recommended for adult patients to exclude important differentials.[15]

Testing for *Helicobacter pylori* infection (urea breath test or stool antigen test) is indicated in patients with appropriate risk factors or in high-prevalence areas (e.g., southern and eastern Europe, South America, and Asia).[15] [17] [18] However, very low platelet counts (i.e., $<10 \times 10^3$/microliter) are not usually observed in patients with H pylori infection, and eradication of infection is not considered curative for ITP.

Quantitative immune globulin level testing is recommended to exclude an immune deficiency syndrome (i.e., common variable immunodeficiency or selective immunoglobulin A [IgA] deficiency), or before treatment with intravenous immune globulin (IVIG). In children, it may be considered at baseline, and should be measured to re-evaluate persistent or chronic ITP.[15]

Pregnancy testing should be considered in women of childbearing age. Thrombocytopenia in pregnancy may be due to a pregnancy-related cause, rather than ITP.[19] Among other possible causes, gestational thrombocytopenia, hypertensive disorders of pregnancy (e.g., pre-eclampsia or hemolysis, elevated liver enzymes, and low platelet count (HELLP) syndrome), and acute fatty liver disease should be considered and excluded. These usually develop in late pregnancy, whereas ITP is the most common cause of thrombocytopenia in early pregnancy. Gestational thrombocytopenia accounts for 70% to 80% of thrombocytopenia in pregnancy.[20]

Other tests to consider

Additional tests may include thyroid function tests (TFTs) and antithyroid antibody tests, because approximately 8% to 14% of patients with ITP develop clinical hyperthyroidism on prolonged follow-up, and patients may develop antibodies to thyroglobulin.[21] Mild thrombocytopenia has been associated with hyperthyroidism (reduced platelet survival) and hypothyroidism (possible decreased platelet production), which may resolve with restoration of the euthyroid status.[15]

History and exam

Key diagnostic factors

bleeding (common)

- Signs of bleeding (e.g., bruising, petechiae, hemorrhagic bullae) can be variable in Immune thrombocytopenia.
- Petechiae are small red or purple spots (around 1-5 mm in diameter) on the skin or mucosal membranes that indicate small capillary hemorrhages. They can appear anywhere on the body, particularly if thrombocytopenia is severe, but are most often found on the lower limbs.
- Hemorrhagic bullae 3-5 mm in diameter on the mucosal surface of the oral cavity and tongue often coexist.
- Minor mucocutaneous bleeding (e.g., bleeding gum) is common, but severe life-threatening bleeding is rare, especially in children.[22]
- Large spontaneous bruising may appear on the arms and legs. Severe disease may be associated with bruising on the torso.
- It is important to differentiate between the mucocutaneous bleeding of thrombocytopenia and the delayed visceral bleeding characteristic of coagulation disorders.
- A history of prior bleeding points to alternative diagnoses.

absence of systemic symptoms (common)

- Specifically, address weight loss, fever, and symptoms of autoimmune disorders such as arthralgias, skin rash, alopecia, and venous thrombosis.
- These symptoms should prompt workup for other pathologies.

absence of medications that cause thrombocytopenia (common)

- Immune thrombocytopenia is a diagnosis of exclusion. The use of heparin, alcohol, quinine/quinidine, sulfa drugs, and many other drugs may cause drug-induced thrombocytopenia.

absent splenomegaly or hepatomegaly (common)

- Less than 3% of patients with Immune thrombocytopenia have splenomegaly. This is similar to the percentage of normal people with a palpable spleen.

absent lymphadenopathy (common)

- Lymphadenopathy should prompt the workup for lymphoproliferative, autoimmune, or infectious etiologies.

Risk factors

Strong

age <5 or >65 years

- Immune thrombocytopenia is more prevalent in males and females younger than 5 years and those older than 65 years.[6] [7] [13]

women of childbearing age

- Immune thrombocytopenia is more prevalent in women of childbearing age.[9][13] [14]

Tests

1st test to order

Test	Result
CBC and peripheral blood smear • Peripheral blood smear distinguishes between true thrombocytopenia and pseudothrombocytopenia (a spuriously low platelet count in blood samples collected into ethylenediaminetetraacetate [EDTA]-containing collection tubes; occurs in about 0.1% of adults; this can be uncovered by a normal platelet count on peripheral blood smear or by using a citrate tube instead of an EDTA tube). • There should be no evidence of myelodysplasia or other disorders (i.e., Pelger-Huet anomaly, nucleated red blood cell, schistocytes, immature granulocytes, large granular lymphocytes). Other cell lines (i.e., red cells and white cells) should be normal.	**platelet count <100 × 10^3/microliter**

Other tests to consider

Test	Result
HIV serology • Routine testing for HIV infection is recommended for adult patients to exclude an important differential.[15]	**negative**
Helicobacter pylori breath test or stool antigen test • Testing for *Helicobacter pylori* infection (urea breath test or stool antigen tests) is indicated in patients with appropriate risk factors or in high-prevalence areas (e.g., southern and eastern Europe, South America, and Asia).[15] [17] [18] However, very low platelet counts (i.e., <10 × 10^3/microliter) are not usually observed in patients with *H pylori* infection.	**negative**
hepatitis C serology • Routine testing for hepatitis C infection is recommended for adult patients to exclude an important differential.[15]	**negative**
thyroid function tests and antithyroid antibody tests • Approximately 8% to 14% of patients with Immune thrombocytopenia develop clinical hyperthyroidism on prolonged follow-up, and patients may develop antibodies to thyroglobulin. • Mild thrombocytopenia has been associated with hyperthyroidism (reduced platelet survival) and hypothyroidism (possible decreased platelet production), which may resolve with restoration of the euthyroid status.[15] • Should be tested before elective splenectomy as it is important to exclude all possible reversible causes of thrombocytopenia before subjecting the patient to the risks of the procedure. • It is not a common enough cause to check on initial laboratory testing if the patient is asymptomatic.	**may be hyper- or hypothyroid**
quantitative immune globulins • Quantitative immune globulin level testing is recommended to exclude an immune deficiency syndrome, or before treatment with intravenous immune globulin. In children, it may be considered at baseline and should be measured to re-evaluate persistent or chronic immune thrombocytopenia.[15]	**may reveal common variable immunodeficiency or selective IgA deficiency**
bone marrow biopsy/aspiration • Only considered if atypical blood film features are present. Not routinely recommended at initial diagnosis, but it may be considered in patients who are unresponsive to medical therapy, or prior to splenectomy.[15]	**increased megakaryocytes; no evidence of malignancy; no flow cytometry or cytogenetic abnormalities**
pregnancy test • Pregnancy testing should be considered in women of childbearing age. Thrombocytopenia in pregnancy may be due to a pregnancy-related cause, rather than immune thrombocytopenia (ITP).[19] Among other possible causes, gestational thrombocytopenia, hypertensive disorders of pregnancy (e.g., pre-eclampsia or hemolysis, elevated liver enzymes, and low platelet count (HELLP) syndrome), and acute fatty liver disease should be considered and excluded. These usually develop in late pregnancy, whereas ITP is the most common cause of thrombocytopenia in early	**may be positive or negative**

Test	Result
pregnancy. Gestational thrombocytopenia accounts for 70% to 80% of thrombocytopenia in pregnancy.[20]	

Differentials

Condition	Differentiating signs / symptoms	Differentiating tests
Pseudothrombocytopenia	• A spuriously low platelet count caused by agglutination when exposed to disodium ethylenediaminetetraacetate occurs in 0.1% of adults. • Prompt recognition of this benign condition avoids exposure to potentially dangerous diagnostic tests and treatments.	• Ex-vivo agglutination, or clumping, can lead to spuriously low platelet counts on automated counters because the machine is unable to detect and count the individual platelets that make up a clump. This may account for up to 15% to 30% of all cases of isolated thrombocytopenia.[23] • Peripheral blood smear shows platelet clumps. • Platelet satellitism, where platelets form a ring around neutrophils, may also be seen.
Congenital thrombocytopenia	• Positive family history of congenital thrombocytopenia. • This is a broad category, which includes MYH9 disorders and several congenital syndromes, such as Paris-Trousseau syndrome. • The bleeding may be worse than expected for the platelet count reported, as platelet function may also be impaired in addition to impaired platelet production. • Congenital disorders may have associated facial dysmorphism, heart defects, intellectual disability, skeletal abnormalities, high-tone sensorineural deafness, nephritis, and cataracts.	• Macrothrombocytes and Dohle body-like inclusions in leukocytes on peripheral blood smear. • A subpopulation of platelets with giant alpha granules is seen in Paris-Trousseau syndrome.
Acquired thrombocytopenia (e.g., related to liver disease or alcohol ingestion)	• Large amounts of alcohol consumption can directly suppress bone marrow production of platelets.[24] Thrombopoietin is produced in the liver, and so severely impaired liver synthetic function can lead to reduced stimulation of platelet production.	• Elevated gamma glutamyl transpeptidase, alkaline phosphatase, alanine aminotransferase, and aspartate aminotransferase. • Prolonged prothrombin time. • Decreased serum albumin. • Megaloblastic peripheral blood smear with macrocytic red blood cell (RBC),

Condition	Differentiating signs / symptoms	Differentiating tests
	• Physical exam may demonstrate signs of liver failure including splenomegaly, ascites, varices, spider angiomata, palmar erythema, and gynecomastia. • Massive splenomegaly from liver disease can lead to exaggerated splenic pooling and thrombocytopenia.	hypersegmented neutrophils, and Howell-Jolly bodies (chromosomal remnants in RBC) suggests vitamin B12 or folate deficiency.
Thrombotic thrombocytopenic purpura	• May demonstrate neurological changes or fever as well as signs of anemia and thrombocytopenia. • Diagnosed during pregnancy or postpartum in 12% to 25% of cases, with 75% of these cases occurring around the time of delivery.[25]	• CBC shows anemia and thrombocytopenia with fragmented red blood cells (schistocytes) on blood smear (microangiopathic film). • Elevated lactate dehydrogenase and low haptoglobin.
Malignant hypertension	• Patients have severely elevated blood pressure.	• CBC shows a microangiopathic picture with anemia, thrombocytopenia, and fragmented red blood cells (schistocytes) on blood smear.
Disseminated intravascular coagulation (DIC)	• DIC is a disorder of coagulation that occurs in the setting of other medical conditions such as sepsis, trauma, malignancy, pregnancy, and amniotic fluid embolism. • Patients are usually very ill with significant bleeding due to coagulation defects.	• CBC shows a microangiopathic picture with anemia, thrombocytopenia, and fragmented red blood cells (schistocytes) on blood smear. • Prolonged prothrombin time and activated partial thromboplastin time. • Elevated D-dimer.
Sepsis	• Patients with sepsis can develop thrombocytopenia. These patients have hypotension and other signs of sepsis. Treatment of the underlying infection should correct the thrombocytopenia.	• Elevated white cell count with left shift. • Peripheral blood smear may show vacuoles in the cytoplasm of neutrophils, which is highly specific for bacteremia. • Blood cultures may be positive. • Thrombocytopenia and anemia are often related to a concurrent DIC phenomenon.

Condition	Differentiating signs / symptoms	Differentiating tests
Gestational thrombocytopenia	• In general, gestational thrombocytopenia is more common and milder than immune thrombocytopenia (ITP). It occurs in late gestation and recovers completely after delivery. • Gestational thrombocytopenia has no risk to the baby, whereas ITP in pregnancy can cause neonatal thrombocytopenia.	• There is no absolute test to differentiate between gestational thrombocytopenia and ITP in pregnancy. Platelet count for gestational thrombocytopenia does not usually fall below 70 × 10^3/microliter. • A platelet count <100 × 10^3/microliter during pregnancy may indicate another underlying cause of thrombocytopenia other than gestational thrombocytopenia, such as ITP.[26]
Myelodysplastic syndromes (MDS)	• MDS is a rare cause of isolated thrombocytopenia. Incidence increases with age, so bone marrow biopsy (which can differentiate immune thrombocytopenia from MDS) is recommended in the workup of patients over 60 years with isolated thrombocytopenia. • Hepatomegaly, splenomegaly, and lymphadenopathy are uncommon but may be present.	• CBC usually shows a decrease in other cell lines, but isolated thrombocytopenia can occur in up to 5% of cases.[27] • Bone marrow core biopsy shows hypercellular marrow. • Bone marrow cytogenetic analysis shows chromosomal abnormalities. • Bone marrow aspirate and trephine shows single or multilineage dysplasia.
Type IIB von Willebrand disease	• Autosomal-dominant disorder, so may have known family history. • A gain-of-function mutation in von Willebrand factor results in binding to platelets and clearance of platelets from the circulation. • These patients have bleeding out of proportion to their platelet count.	• Decreased von Willebrand factor activity. • Increased ristocetin-induced platelet aggregation. • Decreased large von Willebrand factor multimers on electrophoresis.
Splenomegaly/ hypersplenism	• Splenomegaly can lead to a reversible pooling of up to 90% of the total body platelet count, whereas hypersplenism results in early destruction of platelets in the spleen. • Patients may have palpable splenomegaly and signs	• Ultrasound and CT scan will show splenomegaly.

Condition	Differentiating signs / symptoms	Differentiating tests
	of the underlying cause of splenomegaly, such as lymphadenopathy in lymphoma or jaundice and spider nevi in portal hypertension due to liver disease. Consider also a diagnosis of Gaucher disease or other metabolic storage disorders.	
Drug-induced thrombocytopenia	• A thorough medication and herbal supplement history is important for identifying potential offending drugs. • Many drugs have been implicated, including quinidine, quinine, rifampin, and bactrim. Herbal remedies can also be implicated, including tonic water (contains quinine) and tahini (a component of hummus).[28] • Resolution of thrombocytopenia when drug ceased.	• Diagnosis is clinical. • Positive drug-associated antibody test (carried out in specialized laboratories).
Heparin-induced thrombocytopenia (HIT)	• A medication history will reveal the use of heparin or low-molecular-weight heparin. • HIT affects up to 5% of patients exposed to heparin. Thrombocytopenia usually occurs 5 to 14 days after starting heparin therapy (but can occur sooner if there has been a prior heparin exposure). • Up to 55% of patients with untreated HIT will develop thrombosis (e.g., deep vein thrombosis and/or pulmonary embolism).[29]	• Positive for HIT antibodies on anti-platelet factor 4-heparin enzyme-linked immunosorbent assay (ELISA); positive serotonin release assay.
Severe preeclampsia	• New blood pressure elevation and proteinuria after 20 weeks' gestation in pregnant women.	• Elevated urinary protein.
Hemolysis, elevated liver enzymes, and low platelet count (HELLP) syndrome	• Typically, occurs in pregnant women who are already being followed up for gestational hypertension or preeclampsia.	• Low hemoglobin, low haptoglobin, and elevated unconjugated bilirubin consistent with hemolytic anemia.

Condition	Differentiating signs / symptoms	Differentiating tests
	• Patients are hypertensive and may complain of headache, nausea, and abdominal discomfort.	• Elevated LFTs. • Low platelets. • May have abnormal coagulation studies if DIC present.
Acute fatty liver of pregnancy	• A coagulopathy typically precedes the thrombocytopenia.	• Elevated white cell count with left shift. • Total bilirubin increased to levels ≥4 mg/dL. • Hypoglycemia. • Elevated liver enzymes. • Other laboratory abnormalities may include a metabolic acidosis, elevated serum creatinine, elevated BUN, and elevated uric acid.

Criteria

2009 international working group definitions of immune thrombocytopenia (ITP)

The following definitions for ITP have been proposed by an international working group and are used in guidelines:[1] [15]

- Primary ITP: an autoimmune disorder characterized by isolated thrombocytopenia (peripheral blood platelet count <100 × 10^9/L) in the absence of other causes or disorders associated with thrombocytopenia.
- Secondary ITP: all forms of immune-mediated thrombocytopenia except primary ITP.
- Newly diagnosed ITP: within 3 months from diagnosis.
- Persistent ITP: between 3 and 12 months from diagnosis. Includes patients not reaching spontaneous remission or not maintaining complete response without therapy.
- Chronic ITP: lasting for more than 12 months.
- Severe ITP: bleeding symptoms at presentation requiring treatment, or new bleeding symptoms requiring additional therapeutic intervention with a different agent or an increased dose.

Recommendations for target platelet counts before dentistry, surgery, or medical therapy in adults

The exact platelet count needed for any procedure or therapy is unknown, but these consensus-based targets have been proposed as guidance for adults considered to be at "typical" bleeding risk.[15]

- Dentistry:
  - Dental prophylaxis (descaling, deep cleaning): ≥20-30 × 10^3/microliter
  - Simple extractions ≥30 × 10^3/microliter
  - Complex extractions ≥50 × 10^3/microliter
  - Regional dental block ≥30 × 10^3/microliter

- Minor surgery ≥50 × 10^3/microliter
- Major surgery ≥80 × 10^3/microliter
- Major neurosurgery ≥100 × 10^3/microliter
- Vaginal delivery and cesarean section ≥50 × 10^3/microliter
- Spinal or epidural anesthesia ≥80 × 10^3/microliter
- Single antiplatelet agent or anticoagulant: ≥30-50 × 10^3/microliter
- Dual antiplatelet or anticoagulant: ≥50-70 × 10^3/microliter

Screening

Neonates born to a mother with previous or concomitant immune thrombocytopenia are the only population that warrants screening:

- An umbilical cord platelet count is recommended on delivery.
- If levels are low, neonatal platelet count should be repeated as needed; at 3-5 days or, if cord platelet count is <100 × 10^3/microliter, daily until stable.[15]
- The risk of a platelet count <50 × 10^3/microliter in the neonate is approximately 13%, with one third of these patients having bleeding complications.

Approach

Treatment modalities and goals should be individualized, based on the phase of immune thrombocytopenia (ITP), bleeding symptoms and risk, and patient preferences.

Asymptomatic patients may not need treatment and are often managed with close observation. For newly diagnosed patients with bleeding symptoms, corticosteroids are the standard initial treatment; intravenous immune globulin (IVIG) and intravenous Rho(D) immune globulin are also first-line options. Subsequent treatment options for persistent or chronic ITP may include a thrombopoietin receptor agonist, rituximab, or fostamatinib (adults only). Splenectomy may be an option from 12 months after diagnosis. Patients presenting with severe, life- or organ-threatening bleeding require emergency treatment with corticosteroids, IVIG, and platelet transfusion.

Patients should have sufficient platelet levels before undergoing any type of procedure or surgery. Guidelines provide recommendations for target platelet levels for dental procedures and surgery in adults (e.g., minor surgery ≥50 × 10^3/microliter, major surgery ≥80 × 10^3/microliter).[15] See Criteria .

Emergency treatment for adults and children

All adults and children with life- or organ-threatening bleeding, regardless of platelet count, require emergency treatment with a combination of platelet transfusion, a corticosteroid (e.g., prednisone, methylprednisolone, or dexamethasone), and IVIG. A life- or organ- threatening ITP bleed may be at an anatomical site (e.g., intracranial, intraspinal, intraocular, retroperitoneal, pericardial, or intramuscular with compartment syndrome) or a bleed that results in hemodynamic instability or respiratory compromise.[30]

Emergency treatment may take 1-5 days to have an effect, and usually lasts for 2-4 weeks, whether or not the patient has had a prior splenectomy.

Although platelets are likely to be rapidly destroyed during transfusion, there is evidence to suggest that patients with active bleeding respond transiently to transfusion.[31] IVIG can prolong platelet survival; therefore, platelet transfusion may be more effective if given after IVIG infusion.[32] Patients may respond to repeated doses, but this response can diminish over time.

The antifibrinolytic agents aminocaproic acid and tranexamic acid inhibit fibrinolysis and can help stabilize clots that have already formed. These agents can be used as adjunctive treatment as they do not affect platelet count. However, they are contraindicated in patients with hematuria as clots in the collecting system of the kidneys can lead to outlet obstruction.

Thrombopoietin receptor agonists do not act quickly enough to have a role in initial emergency treatment, but they may be considered as a subsequent treatment option if the response to emergency treatment is inadequate, or they may be considered as a concurrent treatment to provide longer-lasting benefit and prevent relapse.[15] [33] [34]

Initial treatment in newly diagnosed adults

The decision to treat should be individualized, taking into account severity of bleeding symptoms, risk of bleeding, risk of side effects from treatment, age, comorbidities, use of antithrombotic medications, lifestyle, and patient preference.[15] [35] Asymptomatic patients do not typically require immediate treatment.[35] However, some patients with a very low platelet count may experience minimal symptoms. Risk of bleeding increases at platelet levels <20 × 10^3/microliter, so a platelet count of 20-30 × 10^3/

microliter is generally chosen as a threshold for treatment in adults.[15] [35] For patients with a platelet count >30 × 10^3/microliter, the risks of morbidity from treatment should be carefully weighed against the potential benefits.[36]

Adults with platelet count ≥30 × 10^3/microliter:

- Asymptomatic adults (or those with only minor mucocutaneous bleeding) who have no additional risk factors do not require immediate treatment; close observation is advised. Clinical follow-up and platelet count are required if bleeding symptoms develop, or prior to surgery or dentistry.
- Adults with bleeding symptoms and/or additional risk factors can be treated first-line with a corticosteroid, IVIG, or intravenous Rho(D) immune globulin, as for adults with platelet count <30 × 10^3/microliter.
- Risk factors may include antithrombotic treatment, requiring an intervention that may cause bleeding, age >60 years, or an occupation or activities with high risk of injury.

Adults with platelet count <30 × 10^3/microliter:

- Patients generally require treatment due to bleeding symptoms or increased risk of bleeding. Corticosteroids, IVIG, and intravenous Rho(D) immune globulin are considered first-line treatments.
- Corticosteroids act against the immune-mediated destruction of platelets in ITP, and they are typically the standard initial treatment. Guidelines recommend a short course (≤6 weeks including treatment and taper) of prednisone or dexamethasone.[15] [35] Generally, patients will show a response within the first 2-3 weeks of corticosteroid therapy. Stopping or tapering corticosteroid treatment too quickly may result in relapse. Prolonging full dose after 4 weeks does not increase the response rate and may cause corticosteroid-related complications.
- IVIG can be used if corticosteroids are contraindicated or not tolerated. If a rapid increase in platelet count is required, IVIG can be given in combination with a corticosteroid.
- Patients who are rhesus (Rh)-positive and nonsplenectomized may benefit from intravenous Rho(D) immune globulin.[37] Intravenous Rho(D) immune globulin can be used first-line in these patients, but treatment response may be transient.[37] Patients develop mild, self-limited hemolysis with this agent, and there is a small risk of severe hemolytic complications, but these are rare.[38] [39] Immediate anaphylactic reactions and hypersensitivity reactions also occur rarely; chills, fever and headaches are more common. Premedication with a corticosteroid may reduce side effects.[15]

The goal of initial treatment is to rapidly obtain a safe platelet count to prevent or stop hemorrhages, and to ensure an acceptable quality of life with minimal treatment-related toxicities. Around 20% to 30% of patients who have initial treatment will not require further therapy.

Treatment in adults with persistent or chronic disease

ITP in adults is often a chronic disease. Spontaneous remission occurs in around 5% to 10% of cases.[40] ITP (i.e., platelet count ≤100 × 10^3/microliter) that does not resolve spontaneously or respond to first-line treatment is defined as:[1]

- Persistent ITP if duration is 3-12 months after diagnosis.
- Chronic ITP if duration is beyond 12 months after diagnosis.

However, the clinical relevance of these definitions is contentious, and subsequent treatment should be individualized.

Some patients with persistent or chronic disease respond to first-line treatments (e.g., corticosteroids and/or IVIG), but they require continuous treatment to achieve a platelet count that is safe. However, prolonged courses of corticosteroids (>6 weeks) are not recommended.[15] [35]

Patients who do not respond to first-line treatment or relapse when corticosteroids are reduced or stopped may be offered a thrombopoietin receptor agonist, rituximab, or fostamatinib as second-line treatment options.

Thrombopoietin receptor agonists:

- Romiplostim, eltrombopag, and avatrombopag are approved for second-line use in chronic ITP. None of these agents shares sequence homology with endogenous thrombopoietin.
- Randomized placebo-controlled trials have shown that each of these agents is effective in increasing platelet count (>50 × 10^3/microliter) in patients with chronic ITP that was unresponsive or relapsed after one or more treatments, including splenectomy (response rates at 1 month >65% for each agent).[35] [41] [42] [43] [44] [45] Reduction or discontinuation of concurrent ITP treatment, and reduction of bleeding, and improvement in health-related quality of life were also reported. Long-term safety and efficacy have been demonstrated for romiplostim and eltrombopag.[46] [47] [48]
- Initial concerns about thrombotic risk, bone marrow reticulin increase, and the potential for promoting neoplasia have lessened.[49] However, rebound thrombocytopenia can be a significant problem with romiplostim if doses are missed.
- In cases of treatment failure or intolerance to one agent, switching to a different thrombopoietin receptor agonist may be effective.[50] One retrospective study showed that switching to avatrombopag was effective following inadequate or poorly tolerated treatment with romiplostim or eltrombopag (93% response rate).[51]
- Thrombopoietin receptor agonists often require indefinite continuous administration as platelet counts tend to return to basal levels after stopping treatment; however, limited data suggests a response can be sustained in 20% to 30% of patients.[50] A dose-reduction regimen and possible discontinuation may be considered in patients who achieve sustained platelet counts >100 × 10^3/microliter and no bleeding for at least 12 months; however, evidence to support this approach is not yet well developed.[52]
- Differences in administration, dietary interactions, and side effects may affect the choice of thrombopoietin receptor agonist. Romiplostim is given weekly by subcutaneous injection. Eltrombopag and avatrombopag are daily oral treatments (although avatrombopag may be administered less frequently in certain patients as part of dose titration). Eltrombopag needs to be taken at least 2 hours before or 4 hours after consuming products containing polyvalent cations (e.g., antacids and dairy products). Treatment with eltrombopag results in hepatotoxicity in approximately 10% of patients, so monthly liver function testing is required. Eltrombopag is an iron chelator, so ferritin and transferrin saturation monitoring may be required for patients with risk factors for iron deficiency (including menstruation).[52]

Rituximab:

- Rituximab is a monoclonal antibody that targets CD20 (a B-cell marker). It has a response rate of approximately 60% in adult patients with ITP.[35][53] [54] [55] Durable response rates are lower for rituximab (39.4%) than for thrombopoietin receptor agonists (63.2%) at 6 months.[35]
- There have been concerns about increased risk of progressive multifocal leukoencephalopathy with rituximab treatment.[56] However, this appears to be extremely rare.[57] Subsequent studies

have reported an acceptable safety profile when used for ITP.[58] Risk of infection is increased, and premedication with a corticosteroid is recommended to prevent acute infusion reactions. Repeated use of rituximab may cause hypogammaglobulinemia.[15]

- Rituximab is contraindicated in patients with active hepatitis B infection because of increased risk of hepatitis B virus reactivation. Patients should be tested for hepatitis B infection before use. Prophylactic antiviral medication and DNA monitoring are required in patients receiving rituximab who have evidence of previous hepatitis B infection. Vaccination may be ineffective in patients treated with rituximab; ideally vaccinations should be given before treatment with rituximab or at least 6 months after the final dose.[15] [59]
- Rituximab is used off-label for ITP.

Fostamatinib:

- Fostamatinib is a spleen tyrosine kinase (Syk) inhibitor approved for second-line use in chronic ITP.
- In two parallel 24-week randomized controlled trials involving adult patients with persistent or chronic ITP who were unresponsive to previous treatments, a stable response (defined as a platelet count ≥50 × 10^3/microliter for ≥4 of 6 biweekly visits, weeks 14-24, without rescue therapy) was achieved in 18% of patients receiving fostamatinib compared with 2% receiving placebo.[60] Most of these patients had received 3 or more previous therapies, and 80% of participants had a duration of ITP of >2 years (median 8.4 years). A post hoc analysis comparing patient subgroups by line of therapy showed a response rate of 78% when fostamatinib was used as second-line therapy and 48% when used as third- or later-line treatment.[61]

The treatment goal for patients with persistent or chronic disease is to increase platelet count to control clinically relevant bleeding or minimize the risk of major bleeding with minimum toxicity while waiting for spontaneous remission or amelioration. However, improvements become much less likely after 12 months from diagnosis.

In cases of treatment failure or intolerance with one second-line drug, switching to another second-line drug or splenectomy (if 12 months or more after diagnosis) may be considered. If treatment with multiple second-line drugs has failed, the following approaches to salvage therapy may be considered:

- Immunosuppressant and immunomodulatory drugs: may be attempted as off-label treatments for ITP. These include azathioprine, cyclosporine, cyclophosphamide, danazol, dapsone, and mycophenolate. However, evidence supporting their use is lacking.[15] [34] Response to mycophenolate may take several weeks, but it appears to be durable.[62] [63] [64] Vinca alkaloids can be given in the acute setting only. Despite a high response rate (with a generally rapid response), use of vinca alkaloids is limited by severe side effects including peripheral neuropathy that may be irreversible.[15] [65]
- Low-dose corticosteroid: may rarely be considered in responsive patients if they can tolerate corticosteroids and they have no contraindications (e.g., diabetes, hypertension, osteoporosis, peptic ulcer). The minimum effective dosage for the shortest time should be used.[15]
- Repeated IVIG infusions: on-demand treatment may be used for responsive patients if tolerated. Most patients respond initially; however, platelet increase is usually transient. There is a need to be vigilant for potential toxicities associated with repeated IVIG infusions, such as renal failure and thrombosis. Hospital attendance as an outpatient is required.

Splenectomy in adults

Splenectomy is considered a second-line treatment, but it is generally deferred until at least 12-24 months after diagnosis to allow for remission or stabilization of platelet count.[15] [35]

The goal of splenectomy is cure or long-lasting remission. A systematic review showed a complete response (i.e., platelet count ≥100 × 10^3/microliter for 30 days or longer with no further treatment for ITP) with splenectomy in around 66% of cases.[66] Splenectomy can be considered if first-line treatments have failed and the patient is deemed suitable for surgery. However, the potential risks and benefits of splenectomy and other second-line treatment options (e.g., rituximab, thrombopoietin receptor agonists, and fostamatinib) should be discussed and a shared decision should be made with the patient. Splenectomy has become less common with the introduction of effective second-line drug options.

Patients with preoperative platelet counts >20 × 10^3/microliter can safely undergo splenectomy. A corticosteroid, IVIG, or thrombopoietin receptor agonist may be used to increase platelet count to a safer level (e.g., >50 × 10^3/microliter) in advance of surgery. In patients with refractory disease who require immediate treatment, splenectomy can be performed if platelet count is ≤20 × 10^3/microliter, and even as low as 5 × 10^3/microliter, as platelet count can quickly increase following clamping of the splenic artery.

At least 2 weeks prior to splenectomy, patients should be immunized with vaccines against *Streptococcus pneumoniae*, *Haemophilus influenzae* type b, and *Neisseria meningitidis*.[67] [68] Local guidance on vaccination pre- and postsplenectomy should be followed.[69] Vaccination may be ineffective for up to 6 months in patients previously treated with rituximab; ideally, vaccinations should be given >6 months before treatment with rituximab or at least 6 months after the final dose.[15] [59] Prophylactic antibiotics should be administered for at least 3 years following splenectomy; some recommend lifelong antibiotic prophylaxis.[67] [70] [71]

Patients who do not respond to splenectomy should be evaluated for an accessory (supernumerary) spleen with radionuclide or magnetic resonance imaging scans, especially if their peripheral blood smear does not show evidence of splenectomy (i.e., Howell-Jolly bodies).

In cases of treatment failure or relapse after splenectomy, a second-line drug may be considered if they have not already been tried.

Treatment in children

ITP is a benign condition for most affected children, and major bleeding (even with prolonged, severe thrombocytopenia) appears to be rare. Most manifestations are limited to the skin.[22] Children often recover spontaneously within weeks or months, with higher rates of spontaneous remission associated with younger age.[72] Studies report complete remission within 6 months in approximately 70% of children with ITP.[73] [74]

Observation is recommended for children who are asymptomatic or have minor bleeding symptoms (e.g., bruising, petechiae, purpura) as the majority will attain a safe platelet count within a few days.[15] It is important to reduce trauma risk in these patients and avoid any antiplatelet medications (e.g., aspirin and nonsteroidal anti-inflammatory drugs). Frequency of monitoring should be individualized, based on bleeding symptoms, platelet counts, and patient preferences.[15] Clinical follow-up and platelet count are required if bleeding symptoms develop, or prior to surgery or dentistry.

Treatment for children with newly diagnosed ITP is only advised in the presence of major bleeding symptoms (e.g., mucosal bleeding):[15] [22] [35]

- A corticosteroid is the usual first-line treatment. Guidelines recommend a short course of prednisone (no longer than 7 days including tapering). Methylprednisolone or dexamethasone are alternative options.[35]

- IVIG or intravenous Rho(D) immune globulin can be used first-line if corticosteroids are contraindicated. Rho(D) immune globulin should only be used in patients who are Rh-positive and nonsplenectomized.[35] [37] IVIG or intravenous Rho(D) immune globulin may be considered in preference to a corticosteroid if a rapid response is required for bleeding symptoms.[15]

Rituximab or a thrombopoietin receptor agonist (eltrombopag or romiplostim) should be considered if there is treatment failure or intolerance with first-line treatments. Eltrombopag and romiplostim are licensed for use in children >1 year of age with chronic ITP that is refractory to other treatments; rituximab is used off-label for ITP.

In a systematic review evaluating rituximab for children with ITP, a platelet count >100 × 10^3/microliter (complete response) was reported in around 39% of children with ITP, and a platelet count >30 × 10^3/microliter (response) was reported in around 68%, with a median response duration of 12.8 months.[75] In a long-term follow-up study, only 26% of children with an initial response to rituximab maintained a treatment-free response after 5 years.[76]

Eltrombopag and romiplostim have been shown in randomized controlled trials to be safe and effective in children ages 1-17 years with persistent or chronic ITP.[77] [78] [79] In these trials, response rates (platelet count ≥50 × 10^3/microliter) 62% and 40% were reported for eltrombopag, and 52% for romiplostim.[77] [78] [79]

One systematic review and meta-analysis comparing thrombopoietin receptor agonists with rituximab in children suggested a similar platelet response rate for each agent. However, more patients maintained a sustainable response with romiplostim, and time to response was lower for eltrombopag and romiplostim (4.75 weeks) than for rituximab (6.75 weeks).[80]

Splenectomy is rarely indicated in childhood ITP. Children with persistent or chronic disease may be candidates for splenectomy if they are unresponsive to, or intolerant of, pharmacologic interventions, and have life-threatening bleeding or substantially impaired health-related quality of life.[15] Splenectomy should be delayed for at least 12 months from diagnosis unless immediate treatment is required (e.g., to improve quality of life).

In children undergoing splenectomy, preoperative prophylaxis with IVIG or oral corticosteroids can be considered to increase platelet count to a safe level and reduce the risk of intraoperative bleeding. At least 2 weeks prior to splenectomy, patients should be immunized with vaccines against *S pneumoniae*, *H influenzae* type b, and *N meningitidis*. Local guidance on vaccination pre- and postsplenectomy should be followed.[81] Vaccination may be ineffective for up to 6 months in patients previously treated with rituximab; ideally vaccinations should be given >6 months before treatment with rituximab or at least 6 months after the final dose.[15] [59] Prophylactic antibiotics should be administered for at least 3 years following splenectomy; some recommend lifelong antibiotic prophylaxis.[67] [70] [71]

ITP in pregnancy

Once a diagnosis of primary ITP has been made, the criteria for starting treatment in pregnancy are the same as for nonpregnant patients.[20] Some treatments used for ITP should be avoided in pregnancy (e.g., fostamatinib, vinca alkaloids and mycophenolate) while others have uncertain safety (e.g., rituximab, and the thrombopoietin receptor agonists). Pregnant patients should be referred to a specialist team including a hematologist and a gynecologist.

A stable platelet count of 20-30 × 10^3/microliter is considered safe during pregnancy until the end of the third trimester when higher levels are needed for delivery. Observation should be considered unless the patient has bleeding symptoms or a procedure is planned.[15] [82]

Initial treatment in pregnancy

If treatment is needed during pregnancy, corticosteroids and IVIG are considered safe first-line treatments:[15] [82]

- Prednisone is usually given as initial therapy (tapered to minimum effective dose). Dexamethasone is not recommended in pregnancy.[82] [83]
- IVIG can be used if corticosteroids are contraindicated or not tolerated. IVIG can be given in combination with prednisone if the response to prednisone is inadequate, a rapid response is needed, or to prepare for delivery.

Intravenous Rho(D) immune globulin may be safe to use in pregnancy for Rh-positive, nonspenectomized women, but evidence is lacking. A small study showed Rho(D) immune globulin was safe and effective for both mother and fetus in the second and third trimester.[84] However, there is an increased risk of hemolysis in both mother and baby.

Treatment of persistent or chronic disease in pregnancy

Pregnant patients with ITP that is unresponsive to initial prednisone or IVIG should be treated with high-dose methylprednisolone, usually in combination with IVIG and/or azathioprine.[15] [85] Azathioprine has been safely used in pregnancy for other indications (e.g., systemic lupus erythematosus or renal transplantation).

There is limited data on the safe use of rituximab in pregnancy, and there are some concerns about pregnancy outcomes after maternal exposure to rituximab.[86] However, guidelines suggest that rituximab can be considered in pregnancy for very severe cases that have not responded to other treatments.[15] Monitoring is required for immunosuppression and infection. Rituximab is used off-label for ITP.

Other immunosuppressive agents, including vinca alkaloids, cyclophosphamide, danazol, and mycophenolate, have been associated with teratogenicity and should not be used.

Thrombopoietin receptor agonists are not currently recommended in pregnancy.

Splenectomy in pregnancy

Splenectomy is rarely performed in pregnant patients; however, if it is required (e.g., for severe refractory disease) and the patient agrees to the procedure, it is best performed early in the second trimester and may be performed laparoscopically.[15] [20]

Patients with preoperative platelet counts >20 × 10^3/microliter can safely undergo splenectomy. Platelet transfusion may be given to increase platelet count if <20 × 10^3/microliter; however, infusions should be carried out with caution as thrombocytosis may occur following splenectomy.

At least 2 weeks prior to splenectomy, patients should be immunized with vaccines against *S pneumoniae*, *H influenzae* type b, and *N meningitidis*.[67] [68] Local guidance on vaccination pre- and postsplenectomy should be followed.[69] Vaccination may be ineffective for up to 6 months in patients previously treated with rituximab; ideally vaccinations should be given >6 months before treatment with

rituximab or at least 6 months after the final dose.[15] [59] Prophylactic antibiotics should be administered for at least 3 years following splenectomy; some recommend lifelong antibiotic prophylaxis.[67] [70] [71]

Preparing for delivery

A target platelet count of ≥50 × 10^3/microliter is usually recommended for vaginal delivery or cesarean section, which may be achieved with prednisone and/or IVIG. If the response to other treatments is inadequate, a thrombopoietin receptor agonist may be considered, although evidence is lacking.[15] See Emerging treatments .

For epidural anesthesia, a target platelet count of ≥80 × 10^3/microliter is recommended, although risk is likely to be low in patients with a platelet count of >70 × 10^3/microliter.[87] If an adequate platelet count has not been achieved and delivery is imminent, platelet transfusion in conjunction with IVIG can be considered.[20]

Treatment algorithm overview

Please note that formulations/routes and doses may differ between drug names and brands, drug formularies, or locations. Treatment recommendations are specific to patient groups: see disclaimer

Initial (summary)		
all patients (child or adult): with life- or organ-threatening bleeding		
	1st	**IVIG plus corticosteroid plus platelet transfusion**
	2nd	**thrombopoietin receptor agonist**
without hematuria	**adjunct**	**antifibrinolytic**

Acute (summary)		
newly diagnosed child		
asymptomatic or with minor bleeding symptoms	1st	observation
with major bleeding symptoms	1st	corticosteroid or IVIG or Rho(D) immune globulin
newly diagnosed adult (pregnant or nonpregnant):		
platelet count ≥30 × 10^3/microliter: asymptomatic without additional risk factors	1st	observation
platelet count ≥30 × 10^3/microliter: with bleeding symptoms and/or additional risk factors	1st	corticosteroid and/or IVIG
	1st	Rho(D) immune globulin
platelet count <30 × 10^3/microliter	1st	corticosteroid and/or intravenous immunoglobulin (IVIG)
	1st	Rho(D) immune globulin

Ongoing (summary)		
child: persistent or chronic disease		
	1st	rituximab
	1st	thrombopoietin receptor agonist
	2nd	splenectomy (plus treatment to achieve target platelet level)
adult nonpregnant: persistent or chronic disease		
	1st	thrombopoietin receptor agonist
	1st	rituximab
	1st	fostamatinib
	2nd	splenectomy (plus treatment to achieve target platelet level)
	3rd	immunosuppressant or immunomodulatory drugs
	3rd	low-dose corticosteroid or repeated IVIG infusions
pregnant: persistent or chronic disease		
	1st	high-dose methylprednisolone
	adjunct	IVIG and/or azathioprine
	2nd	rituximab
	2nd	splenectomy

Treatment algorithm

Please note that formulations/routes and doses may differ between drug names and brands, drug formularies, or locations. Treatment recommendations are specific to patient groups: see disclaimer

Initial

all patients (child or adult): with life- or organ-threatening bleeding

1st **IVIG plus corticosteroid plus platelet transfusion**

Primary options

» immune globulin (human): children and adults: 1 g/kg intravenously as a single dose, a second dose may be given if there is a poor response to initial treatment

--AND--

» prednisone: children: 2-4 mg/kg/day orally given in 3-4 divided doses for 5-7 days, maximum 120 mg/day; adults: 0.5 to 2 mg/kg/day orally for 1-3 weeks followed by a gradual taper, maximum 80 mg/day

-or-

» methylprednisolone sodium succinate: children: 30 mg/kg intravenously every 24 hours for 3 days, followed by treatment with an oral corticosteroid as clinically indicated, maximum 1000 mg/dose; adults: 1000 mg intravenously every 24 hours for 3 days, followed by treatment with an oral corticosteroid as clinically indicated

-or-

» dexamethasone: children: 0.6 mg/kg orally once daily for 4 days, may repeat course, maximum 40 mg/day; adults: 40 mg orally once daily for 4 days, may repeat course

» All adults and children with life- or organ-threatening bleeding, regardless of platelet count, require emergency treatment with a combination of platelet transfusion, a corticosteroid, and intravenous immune globulin (IVIG).

» A life- or organ-threatening immune thrombocytopenia bleed may be at an anatomical site (e.g., intracranial, intraspinal, intraocular, retroperitoneal, pericardial, or intramuscular with compartment syndrome) or a bleed that results in hemodynamic instability or respiratory compromise.[30]

» Emergency treatment may take 1-5 days to have an effect, and usually lasts for 2-4 weeks,

Initial

whether or not the patient has had a prior splenectomy.

» Although platelets are likely to be rapidly destroyed during transfusion, there is evidence to suggest that patients with active bleeding respond transiently to transfusion.[31] IVIG can prolong platelet survival; therefore, platelet transfusion may be more effective if given after IVIG infusion.[32]

» Patients may respond to repeated doses, but this response can diminish over time.

2nd **thrombopoietin receptor agonist**

Primary options

» eltrombopag: children 1-5 years of age: 25-75 mg orally once daily, adjust dose according to response; children ≥6 years of age and adults: 50-75 mg orally once daily, adjust dose according to response

OR

» romiplostim: children ≥1 year of age and adults: 1-10 micrograms/kg subcutaneously once weekly, adjust dose according to response

OR

» avatrombopag: adults: 20-40 mg orally once daily, adjust dose according to response

» Thrombopoietin receptor agonists do not act quickly enough to have a role in initial emergency treatment, but they may be considered as a subsequent option if the response to emergency treatment is inadequate, or they may be considered concurrently with emergency treatment to provide longer-lasting benefit and prevent relapse.[15] [33] [34]

without hematuria **adjunct** **antifibrinolytic**

Treatment recommended for SOME patients in selected patient group

Primary options

» aminocaproic acid: children: 100 mg/kg intravenously as a loading dose initially, followed by 33.3 mg/kg/hour infusion, maximum 30 g/day; adults: 4-5 g intravenously as a loading dose initially, followed by 1 g/hour infusion, maximum 30 g/day

Initial

OR

» tranexamic acid: adults: 0.5 to 1 g orally three times daily

» Aminocaproic acid and tranexamic acid inhibit fibrinolysis and can help to stabilize clots that have already formed. These agents can be used as adjunctive treatment as they do not affect platelet count.

» Aminocaproic acid and tranexamic acid are contraindicated in patients with hematuria because clots in the collecting system of the kidneys can lead to outlet obstruction.

Acute

newly diagnosed child

asymptomatic or with minor bleeding symptoms

1st **observation**

» Observation is recommended for children who are asymptomatic or have minor bleeding symptoms (e.g., bruising, petechiae, purpura) as the majority will attain a safe platelet count within a few days.[15]

» It is important to reduce trauma risk in children, and avoid any antiplatelet medications (e.g., aspirin and nonsteroidal anti-inflammatory drugs).

» Frequency of monitoring should be individualized, based on bleeding symptoms, platelet counts, and patient preferences.[15] Clinical follow-up and platelet count are required if bleeding symptoms develop or prior to surgery or dentistry. Patients should have sufficient platelet levels before undergoing any type of procedure or surgery.[15]

» Immune thrombocytopenia is a benign condition for most affected children, and major bleeding (even with prolonged, severe thrombocytopenia) appears to be rare.[22] Most manifestations are limited to the skin.

» Children often recover spontaneously within weeks or months, with higher rates of spontaneous remission associated with younger age.[72] Studies report complete remission within 6 months in approximately 70% of children with ITP.[73] [74]

with major bleeding symptoms

1st **corticosteroid or IVIG or Rho(D) immune globulin**

Primary options

» prednisone: 2-4 mg/kg/day orally given in 3-4 divided doses for 5-7 days, maximum 120 mg/day

OR

» methylprednisolone sodium succinate: 30 mg/kg intravenously every 24 hours for 3 days, followed by treatment with an oral corticosteroid as clinically indicated, maximum 1000 mg/dose

OR

Acute

» dexamethasone: 0.6 mg/kg orally once daily for 4 days, may repeat course, maximum 40 mg/day

Secondary options

» immune globulin (human): 1 g/kg intravenously as a single dose, a second dose may be given if there is a poor response to initial treatment

OR

» Rho(D) immune globulin: consult specialist for guidance on dose

» Treatment for children with newly diagnosed immune thrombocytopenia is only advised in the presence of major bleeding symptoms (e.g., mucosal bleeding).[15] [22][35]

» A corticosteroid is the usual first-line treatment. Guidelines recommend a short course of prednisone (no longer than 7 days including tapering). Methylprednisolone or dexamethasone are alternative options.[35]

» Intravenous immune globulin (IVIG) or intravenous Rho(D) immune globulin can be used first-line if corticosteroids are contraindicated. Rho(D) immune globulin should only be used in patients who are Rh-positive and nonsplenectomized.[35] [37] IVIG or intravenous Rho(D) immune globulin may be considered in preference to a corticosteroid if a rapid response is required for bleeding symptoms.[15]

» Patients develop mild, self-limited hemolysis on treatment with Rho(D) immune globulin, and there is a small risk of severe hemolysis and renal failure, but these are rare.[38] [39] Immediate anaphylactic reactions and hypersensitivity reactions can also occur, and headaches are commonly reported. Steroid premedication may reduce side effects.[15]

» Patients should have sufficient platelet levels before undergoing any type of procedure or surgery.[15]

newly diagnosed adult (pregnant or nonpregnant):

- **platelet count ≥30 × 10^3/microliter: asymptomatic without additional risk factors**

1st

observation

» Asymptomatic adults (or those with only minor mucocutaneous bleeding) with platelet count

MANAGEMENT

Acute

≥30 × 10^3/microliter who have no additional risk factors do not require immediate treatment; close observation is advised.

» Risk factors may include antithrombotic treatment, requiring an intervention that may cause bleeding, age >60 years, or an occupation or activities with high risk of injury.

» Immune thrombocytopenia in adults is often a chronic disease. Spontaneous remission occurs in around 5% to 10% of cases.[40] Clinical follow-up and platelet count are required if bleeding symptoms develop or prior to surgery or dentistry.

» The goal of initial treatment is to rapidly obtain a safe platelet count to prevent or stop hemorrhages, and to ensure an acceptable quality of life with minimal treatment-related toxicities. Around 20% to 30% of patients who have initial treatment will not require further therapy.

» Patients should have sufficient platelet levels before undergoing any type of procedure or surgery. Guidelines provide recommendations for target platelet levels for dental procedures and surgery in adults (e.g., minor surgery ≥50 × 10^3/microliter, major surgery ≥80 × 10^3/microliter).[15]

» The criteria for starting treatment in pregnancy are the same as for nonpregnant patients.[20] Pregnant patients should be referred to a team including a hematologist and a gynecologist.

» A stable platelet count of 20-30 × 10^3/microliter is considered safe during pregnancy until the end of the third trimester when higher levels are needed for delivery. Observation should be considered unless the patient has bleeding symptoms or a procedure is planned.[15] [82] A target platelet count of ≥50 × 10^3/microliter is recommended for vaginal delivery or cesarean section. For epidural anesthesia, a target platelet count of ≥80 × 10^3/microliter is recommended, although risk is likely to be low in patients with a platelet count of >70 × 10^3/microliter.[87]

platelet count ≥30 × 10^3/microliter: with bleeding symptoms and/or additional risk factors — **1st** — **corticosteroid and/or IVIG**

Primary options

» prednisone: 0.5 to 2 mg/kg/day orally for 1-3 weeks followed by a gradual taper, maximum 80 mg/day
-or-

Acute

» methylprednisolone: 1000 mg intravenously every 24 hours for 3 days, followed by treatment with an oral corticosteroid as clinically indicated

-or-

» dexamethasone: 40 mg orally once daily for 4 days, may repeat course

--AND/OR--

» immune globulin (human): 1 g/kg intravenously as a single dose, a second dose may be given if there is a poor response to initial treatment

» Newly diagnosed adults with platelet count ≥30 × 10^3/microliter who have bleeding symptoms (e.g., bruising, petechiae, purpura, oral mucosal bleeding, epistaxis) and/or additional risk factors can be treated first-line with a corticosteroid and/or intravenous immune globulin (IVIG).

» Risk factors may include antithrombotic treatment, requiring an intervention that may cause bleeding, age >60 years, or high-injury risk occupation or activities.

» For patients with a platelet count above >30 × 10^3/microliter, the risks of morbidity from treatment should be carefully weighed against the potential benefits.[36]

» Corticosteroids act against the immune-mediated destruction of platelets in immune thrombocytopenia, and they are typically the standard initial treatment. For nonpregnant patients, guidelines recommend a short course (≤6 weeks including treatment and taper) of prednisone or dexamethasone.[15] [35] Generally, patients will show a response within the first 2-3 weeks of corticosteroid therapy. Stopping or tapering corticosteroid treatment too quickly may result in relapse. Prolonging full dose after 4 weeks does not increase the response rate and may cause corticosteroid-related complications.

» IVIG can be used if corticosteroids are contraindicated or not tolerated. If a rapid increase in platelet count is required, IVIG can be given in combination with a corticosteroid.

» If treatment is needed during pregnancy, corticosteroids and IVIG are considered safe first-line treatments.[15] [82] Prednisone is usually given as initial therapy (tapered to minimum effective dose). Dexamethasone is not recommended in pregnancy.[82] [83] IVIG can be used if corticosteroids are contraindicated or

Acute

not tolerated. IVIG can be given in combination with prednisone if the response to prednisone is inadequate, a rapid response is needed, or to prepare for delivery.

» Patients should have sufficient platelet levels before undergoing any type of procedure or surgery. Guidelines provide recommendations for target platelet levels for dental procedures and surgery in adults (e.g., minor surgery ≥50 × 10^3/microliter, major surgery ≥80 × 10^3/microliter).[15] In pregnant women, a target platelet count of ≥50 × 10^3/microliter is recommended for vaginal delivery and cesarean section. For epidural anesthesia, a target platelet count of ≥80 × 10^3/microliter is recommended, although risk is likely to be low in patients with a platelet count of >70 × 10^3/microliter.[87]

» The goal of initial treatment is to rapidly obtain a safe platelet count to prevent or stop hemorrhages, and to ensure an acceptable quality of life with minimal treatment-related toxicities. Around 20% to 30% of patients who have initial treatment will not require further therapy.

1st **Rho(D) immune globulin**

Primary options

» Rho(D) immune globulin: consult specialist for guidance on dose

» Patients who are rhesus (Rh)-positive and nonsplenectomized may benefit from intravenous Rho(D) immune globulin.[37] Intravenous Rho(D) immune globulin can be used first-line in these patients, but treatment response may be transient.[37]

» Rho(D) immune globulin may be safe to use in pregnancy, but evidence is lacking. In a small study involving Rh-positive and nonsplenectomized pregnant patients, Rho(D) immune globulin was shown to be safe and effective for both mother and fetus in the second and third trimester.[84] However, there is an increased risk of hemolysis in both mother and baby.

» Patients develop mild, self-limited hemolysis with Rho(D) immune globulin, and there is a small risk of severe hemolytic complications, but these are rare.[38] [39] Immediate anaphylactic reactions also occur rarely; chills, fever and headaches are more common. Premedication with a corticosteroid may reduce side effects.[15]

Acute

» Patients should have sufficient platelet levels before undergoing any type of procedure or surgery. Guidelines provide recommendations for target platelet levels for dental procedures and surgery in adults (e.g., minor surgery ≥50 × 10^3/microliter, major surgery ≥80 × 10^3/microliter).[15] In pregnant women, a target platelet count of ≥50 × 10^3/microliter is recommended for vaginal delivery or cesarean section. For epidural anesthesia, a target platelet count of ≥80 × 10^3/microliter is recommended, although risk is likely to be low in patients with a platelet count of >70 × 10^3/microliter.[87]

platelet count <30 × 10^3/microliter — **1st** — **corticosteroid and/or intravenous immunoglobulin (IVIG)**

Primary options

» prednisone: 0.5 to 2 mg/kg/day orally for 1-3 weeks followed by a gradual taper, maximum 80 mg/day
-or-
» methylprednisolone: 1000 mg intravenously every 24 hours for 3 days, followed by treatment with an oral corticosteroid as clinically indicated
-or-
» dexamethasone: 40 mg orally once daily for 4 days, may repeat course

--AND/OR--

» immune globulin (human): 1 g/kg intravenously as a single dose, a second dose may be given if there is a poor response to initial treatment

» Newly diagnosed adults with a platelet count <30 × 10^3/microliter generally require treatment due to bleeding symptoms or increased risk of bleeding.[35]

» A corticosteroid and/or intravenous immune globulin (IVIG) are considered first-line treatments.

» Corticosteroids act against the immune-mediated destruction of platelets in immune thrombocytopenia, and they are typically the standard initial treatment.[88] For non-pregnant patients, guidelines recommend a short course (≤6 weeks including treatment and taper) of prednisone or dexamethasone.[15] [35] Generally, patients will show a response within the first 2-3 weeks of corticosteroid therapy. Stopping or tapering corticosteroid treatment too quickly may result in relapse. Prolonging full dose after 4 weeks does not increase the

Acute

response rate and may cause corticosteroid-related complications.

» IVIG can be used if corticosteroids are contraindicated. If a rapid increase in platelet count is required, IVIG can be given in combination with a corticosteroid.

» If treatment is needed during pregnancy, corticosteroids and IVIG are considered safe first-line treatments.[15] [82] Prednisone is usually given as initial therapy (tapered to minimum effective dose). Dexamethasone is not recommended in pregnancy.[83] IVIG can be used if corticosteroids are contraindicated or not tolerated. IVIG can be given in combination with prednisone if the response to prednisone is inadequate, a rapid response is needed, or to prepare for delivery.

» Patients should have sufficient platelet levels before undergoing any type of procedure or surgery. Guidelines provide recommendations for target platelet levels for dental procedures and surgery in adults (e.g., minor surgery ≥50 × 10^3/microliter, major surgery ≥80 × 10^3/microliter).[15] In pregnant women, a target platelet count of ≥50 × 10^3/microliter is recommended for vaginal delivery and cesarean section. For epidural anesthesia, a target platelet count of ≥80 × 10^3/microliter is recommended, although risk is likely to be low in patients with a platelet count of >70 × 10^3/microliter.[87]

» The goal of initial treatment is to rapidly obtain a safe platelet count to prevent or stop hemorrhages, and to ensure an acceptable quality of life with minimal treatment-related toxicities. Around 20% to 30% of patients who have initial treatment will not require further therapy.

1st **Rho(D) immune globulin**

Primary options

» Rho(D) immune globulin: consult specialist for guidance on dose

» Patients who are rhesus (Rh)-positive and nonsplenectomized may benefit from intravenous Rho(D) immune globulin, which has been shown to increase platelet count in more than 70% of cases (including both children and adults).[37] Intravenous Rho(D) immune globulin can be used first-line in these patients, but treatment response may be transient.[37]

Acute

» Rho(D) immune globulin may be safe to use in pregnancy, but evidence is lacking. In a small study involving Rh-positive and nonsplenectomized pregnant patients, Rho D immune globulin was shown to be safe and effective for both mother and fetus in the second and third trimester.[84] However, there is an increased risk of hemolysis in both mother and baby.

» Patients develop mild, self-limited hemolysis on treatment with Rho(D) immune globulin, and there is a small risk of severe hemolytic complications, but these are rare.[38] [39] Immediate anaphylactic reactions and hypersensitivity reactions also occur rarely; chills, fever, and headaches are more common. Premedication with a corticosteroid may reduce side effects.[15]

» Patients should have sufficient platelet levels before undergoing any type of procedure or surgery. Guidelines provide recommendations for target platelet levelsfor dental procedures and surgery in adults (e.g., minor surgery ≥50 × 10^3/microliter, major surgery ≥80 × 10^3/microliter).[15] In pregnant women, a target platelet count of ≥50 × 10^3/microliter is recommended for vaginal delivery or cesarean section. For epidural anesthesia, a target platelet count of ≥80 × 10^3/microliter is recommended, although risk is likely to be low in patients with a platelet count of >70 × 10^3/microliter.[87]

Ongoing

child: persistent or chronic disease

1st **rituximab**

Primary options

» rituximab: 375 mg/square meter of body surface area intravenously once weekly for 4 doses

» Immune thrombocytopenia (ITP; i.e., platelet count ≤100 × 10^3/microliter) that does not resolve spontaneously or respond to first-line treatment is defined as persistent ITP if duration is 3-12 months after diagnosis and chronic ITP if duration is beyond 12 months after diagnosis.

» Rituximab should be considered if there is treatment failure or intolerance with first-line treatments (e.g., corticosteroids, IVIG). Rituximab is used off-label for ITP.

» In a systematic review evaluating rituximab for children with ITP, a platelet count >100 × 10^3/microliter (complete response) was reported in around 39% of children with ITP, and a platelet count >30 × 10^3/microliter (response) was reported in around 68%, with a median response duration of 12.8 months.[75] However, only 26% of patients (children and adults) treated with rituximab continue to have In a long-term follow-up study, only 26% of children with an initial response to rituximab treatment maintained a treatment-free response after 5 years.[76]

» The treatment goal is to increase platelet count to control clinically relevant bleeding or minimize the risk of major bleeding with minimum toxicity while waiting for spontaneous remission or amelioration.

» In cases of treatment failure or intolerance with rituximab, switching to another second-line drug (e.g., a thrombopoietin receptor agonists [eltrombopag or romiplostim]) may be considered.

» Patients should have sufficient platelet levels before undergoing any type of procedure or surgery.[15]

1st **thrombopoietin receptor agonist**

Primary options

» eltrombopag: children 1-5 years of age: 25-75 mg orally once daily, adjust dose according to response; children ≥6 years of

Ongoing

age: 50-75 mg orally once daily, adjust dose according to response

OR

» romiplostim: children ≥1 year of age: 1-10 micrograms/kg subcutaneously once weekly, adjust dose according to response

» Immune thrombocytopenia (ITP; i.e., platelet count ≤100 × 10^3/microliter) that does not resolve spontaneously or respond to first-line treatment is defined as persistent ITP if duration is 3-12 months after diagnosis and chronic ITP if duration is beyond 12 months after diagnosis.

» A thrombopoietin receptor agonist (eltrombopag or romiplostim) should be considered if there is treatment failure or intolerance with first-line treatments (e.g., corticosteroids, IVIG).

» Eltrombopag and romiplostim are licensed for use in children >1 year of age with chronic ITP that is refractory to other treatments (e.g., corticosteroids, IVIG).

» Eltrombopag and romiplostim have been shown in randomized controlled trials to be safe and effective in children ages 1-17 years with persistent or chronic ITP.[77] [78][79] In these trials, response rates (platelet count ≥50 × 10^3/microliter) of 62% and 40% were reported for eltrombopag, and 52% for romiplostim.[77] [78] [79]

» One systematic review and meta-analysis comparing thrombopoietin receptor agonists with rituximab in children suggested a similar platelet response rate for each agent. However, more patients maintained a sustainable response with romiplostim, and time to response was lower for eltrombopag and romiplostim (4.75 weeks) than for rituximab (6.75 weeks).[80]

» The treatment goal is to increase platelet count to control clinically relevant bleeding or minimize the risk of major bleeding with minimum toxicity while waiting for spontaneous remission or amelioration.

» In cases of treatment failure or intolerance with thrombopoietin receptor agonists, switching to another second-line drug (e.g., rituximab) may be considered.

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» Patients should have sufficient platelet levels before undergoing any type of procedure or surgery.[15]

2nd **splenectomy (plus treatment to achieve target platelet level)**

» Immune thrombocytopenia (ITP; i.e., platelet count ≤100 × 10^3/microliter) that does not resolve spontaneously or respond to first-line treatment is defined as persistent ITP if duration is 3-12 months after diagnosis and chronic ITP if duration is beyond 12 months after diagnosis.[1]

» Splenectomy is rarely indicated in childhood ITP. Children with persistent or chronic disease may be candidates for splenectomy if they are unresponsive to, or intolerant of, pharmacologic interventions, and have life-threatening bleeding or substantially impaired health-related quality of life.[15] Splenectomy should be delayed for at least 12 months unless immediate treatment is required (e.g., to improve quality of life).

» In children undergoing splenectomy, preoperative prophylaxis with IVIG or oral corticosteroids can be considered to increase platelet count to a safe level and reduce the risk of intraoperative bleeding.

» At least 2 weeks prior to splenectomy, patients should be immunized with vaccines against *Streptococcus pneumoniae* , *Haemophilus influenzae* type b, and *Neisseria meningitidis* . Local guidance on vaccination pre- and postsplenectomy should be followed.[81] Vaccination may be ineffective for up to 6 months in patients previously treated with rituximab; ideally vaccinations should be given >6 months before treatment with rituximab or at least 6 months after the final dose.[15] [59] Prophylactic antibiotics should be administered for at least 3 years following splenectomy; some recommend lifelong antibiotic prophylaxis.[67] [70] [71]

» The goal of splenectomy is cure or long-lasting remission.

» Patients who do not respond to splenectomy should be evaluated for an accessory (supernumerary) spleen with radionuclide or MRI scans especially if their peripheral blood smear does not show evidence of splenectomy (i.e., Howell-Jolly bodies).

adult nonpregnant: persistent or chronic disease

Ongoing

1st **thrombopoietin receptor agonist**

Primary options

» romiplostim: 1-10 micrograms/kg subcutaneously once weekly, adjust dose according to response

OR

» eltrombopag: 50-75 mg orally once daily, adjust dose according to response

OR

» avatrombopag: 20-40 mg orally once daily, adjust dose according to response

» Immune thrombocytopenia (ITP; i.e., platelet count ≤100 × 10^3/microliter) that does not resolve spontaneously or respond to first-line treatment is defined as persistent ITP if duration is 3-12 months after diagnosis, and chronic ITP if duration is beyond 12 months after diagnosis.[1]

» Patients who do not respond to first-line treatment or relapse when corticosteroids are reduced or stopped may be offered a thrombopoietin receptor agonist as a second-line treatment option.

» Romiplostim, eltrombopag, and avatrombopag are approved for second-line use in chronic ITP. None of these agents shares sequence homology with endogenous thrombopoietin.

» Randomized placebo-controlled trials have shown that each of these agents is effective in increasing platelet count (>50 × 10^3/microliter) in patients with chronic ITP that was unresponsive or relapsed after one or more treatments, including splenectomy (response rates at 1 month >65% for each agent).[35] [41] [42] [43] [44] [45] Reduction or discontinuation of concurrent ITP treatment, and reduction of bleeding, and improvement in health-related quality of life were also reported. Long-term safety and efficacy have been demonstrated for romiplostim and eltrombopag.[46] [47][48]

» Initial concerns about thrombotic risk, bone marrow reticulin increase, and the potential for promoting neoplasia have lessened.[49] However, rebound thrombocytopenia can be a significant problem with romiplostim if doses are missed.

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» In cases of treatment failure or intolerance to one agent, switching to a different thrombopoietin receptor agonist may be effective.[50] One retrospective study showed that switching to avatrombopag was effective following inadequate or poorly tolerated treatment with romiplostim or eltrombopag (93% response rate).[51]

» Thrombopoietin receptor agonists often require indefinite continuous administration as platelet counts tend to return to basal levels after stopping treatment; however, limited data suggests a response can be sustained in 20% to 30% of patients.[50] A dose-reduction regimen and possible discontinuation may be considered in patients who achieve sustained platelet counts >100 × 10^3/microliter and no bleeding for at least 12 months; however, evidence to support this approach not yet well developed.[52]

» Differences in administration, dietary interactions, and side effects may affect the choice of thrombopoietin receptor agonist. Romiplostim is given once a week by subcutaneous injection. Eltrombopag and avatrombopag are once-daily oral treatments (although avatrombopag may be administered less frequently in certain patients as part of dose titration). Eltrombopag needs to be taken at least 2 hours before or 4 hours after consuming products containing polyvalent cations (e.g., antacids and dairy products). Treatment with eltrombopag results in hepatotoxicity in approximately 10% of patients, so monthly liver function testing is required. Eltrombopag is an iron chelator, so ferritin and transferrin saturation monitoring may be required for patients with risk factors for iron deficiency (including menstruation).[52]

» The treatment goal for patients with persistent or chronic disease is to increase platelet count to control clinically relevant bleeding or minimize the risk of major bleeding with minimum toxicity while waiting for spontaneous remission or amelioration. However, improvements become much less likely after more than 12 months from diagnosis.

» In cases of treatment failure or intolerance with one second-line drug, switching to another second-line drug, or splenectomy (if 12 months or more after diagnosis) may be considered.

» Patients should have sufficient platelet levels before undergoing any type of procedure or surgery. Guidelines provide recommendations

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for target platelet levels for dental procedures and surgery in adults (e.g., minor surgery ≥50 × 10^3/microliter, major surgery ≥80 × 10^3/microliter).[15]

1st **rituximab**

Primary options

» rituximab: 375 mg/square meter of body surface area intravenously once weekly for 4 doses

» Immune thrombocytopenia (ITP; i.e., platelet count ≤100 × 10^3/microliter) that does not resolve spontaneously or respond to first-line treatment is defined as persistent ITP if duration is 3-12 months after diagnosis and chronic ITP if duration is beyond 12 months after diagnosis.[1]

» Patients who do not respond to first-line treatment or relapse when corticosteroids are reduced or stopped may be offered rituximab as a second-line treatment option.

» Rituximab is a monoclonal antibody that targets CD20 (a B-cell marker). It has a response rate of approximately 60% in adult patients with ITP.[35] [53] [54] [55] Durable response rates are lower for rituximab (39.4%) than thrombopoietin receptor agonists (63.2%) at 6 months.[35]

» There have been concerns about increased risk of progressive multifocal leukoencephalopathy with rituximab treatment.[56] However, this appears to be extremely rare.[57] Subsequent studies have reported an acceptable safety profile when used for ITP.[58] Risk of infection is increased, and steroid premedication is recommended to prevent acute infusion reactions. Repeated use of rituximab may cause hypogammaglobulinemia.[15]

» Rituximab is contraindicated in patients with active hepatitis B infection because of increased risk of hepatitis B virus reactivation. Patients should be tested for hepatitis B infection before use. Prophylactic antiviral medication and DNA monitoring are required in patients receiving rituximab who have evidence of previous hepatitis B infection. Vaccination may be ineffective for up to 6 months in patients previously treated with rituximab; ideally, vaccinations should be given >6 months before treatment with rituximab.[15] [59]

» Rituximab is used off-label for ITP.

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» The treatment goal for patients with persistent or chronic disease is to increase platelet count to control clinically relevant bleeding or minimize the risk of major bleeding with minimum toxicity while waiting for spontaneous remission or amelioration. However, improvements become much less likely after more than 12 months from diagnosis.

» In cases of treatment failure or intolerance with one second-line drug, switching to another second-line drug, or splenectomy (if 12 months or more after diagnosis) may be considered.

» Patients should have sufficient platelet levels before undergoing any type of procedure or surgery. Guidelines provide recommendations for target platelet levels (e.g., minor surgery ≥50 × 10^3/microliter, major surgery ≥80 × 10^3/microliter).[15]

1st **fostamatinib**

Primary options

» fostamatinib: 100-150 mg orally twice daily, adjust dose according to response

» Immune thrombocytopenia (ITP; i.e., platelet count ≤100 × 10^3/microliter) that does not resolve spontaneously or respond to first-line treatment is defined as persistent ITP if duration is 3-12 months after diagnosis and chronic ITP if duration is beyond 12 months after diagnosis.[1]

» Patients who do not respond to first-line treatment or relapse when corticosteroids are reduced or stopped may be offered fostamatinib as a second-line treatment option.

» Fostamatinib is a spleen tyrosine kinase (Syk) inhibitor approved for second-line use in chronic ITP.

» In two parallel 24-week randomized controlled trials involving adult patients with persistent or chronic ITP who were unresponsive to previous treatments, a stable response (i.e., platelet count ≥50 × 10^3/microliter for 4 of 6 weeks) was achieved in 18% of patients receiving fostamatinib compared with 2% receiving placebo.[60] Most of these patients had received 3 or more previous therapies, and 80% of participants had a duration of ITP of >2 years (median 8.4 years). A post hoc analysis comparing patient subgroups by line of therapy showed a response rate of 78% when fostamatinib was used as second-line

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therapy and 48% when used as third- or later-line treatment.[61]

» The treatment goal for patients with persistent or chronic disease is to increase platelet count to control clinically relevant bleeding or minimize the risk of major bleeding with minimum toxicity while waiting for spontaneous remission or amelioration. However, improvements become much less likely after more than 12 months from diagnosis.

» In cases of treatment failure or intolerance with one second-line drug, switching to another second-line drug, or splenectomy (if 12 months or more after diagnosis) may be considered.

» Patients should have sufficient platelet levels before undergoing any type of procedure or surgery. Guidelines provide recommendations for target platelet levels (e.g., minor surgery ≥50 × 10^3/microliter, major surgery ≥80 × 10^3/microliter).[15]

2nd **splenectomy (plus treatment to achieve target platelet level)**

» Splenectomy is considered a second-line treatment, but it is generally deferred until at least 12-24 months after diagnosis to allow for remission or stabilization of platelet count.

» The goal of splenectomy is cure or long-lasting remission. A systematic review showed a complete response (i.e., platelet count ≥100 × 10^3/microliter for 30 days or longer with no further treatment for immune thrombocytopenia) with splenectomy in around 66% of cases.[66] Splenectomy can be considered if first-line treatments have failed and the patient is deemed suitable for surgery. However, the potential risks and benefits of splenectomy and other second-line treatment options (e.g., rituximab, thrombopoietin receptor agonists, and fostamatinib) should be discussed and a shared decision should be made with the patient. Splenectomy has become less common with the introduction of effective second-line drug options.

» Patients with preoperative platelet counts >20 × 10^3/microliter can safely undergo splenectomy. A corticosteroid, IVIG, or thrombopoietin receptor agonist may be used to increase platelet count to a safer level (e.g., >50 × 10^3/microliter) in advance of surgery. In patients with refractory disease who require immediate treatment, splenectomy can be performed if

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platelet count is ≤20 × 10^3/microliter, and even as low as 5 × 10^3/microliter, as platelet count can quickly increase following clamping of the splenic artery.

» At least 2 weeks prior to splenectomy, patients should be immunized with vaccines against *S pneumoniae* , *H influenzae* type b, and *N meningitidis* .[67] [68] Local guidance on vaccination pre- and postsplenectomy should be followed.[69] Vaccination may be ineffective for up to 6 months in patients previously treated with rituximab; ideally, vaccinations should be given >6 months before treatment with rituximab or at least 6 months after the final dose.[15] [59] Prophylactic antibiotics should be administered for at least 3 years following splenectomy; some recommend lifelong antibiotic prophylaxis.[67] [70] [71]

» Patients who do not respond to splenectomy should be evaluated for an accessory (supernumerary) spleen with radionuclide or magnetic resonance imaging scans, especially if their peripheral blood smear does not show evidence of splenectomy (i.e., Howell-Jolly bodies).

» In cases of treatment failure or relapse after splenectomy, a second-line drug may be considered if they have not already been tried.

3rd **immunosuppressant or immunomodulatory drugs**

Primary options

» azathioprine: 50-200 mg/day orally

OR

» cyclosporine modified: 3-6 mg/kg/day orally initially, adjust dose according to response, maximum 200 mg/day

OR

» cyclophosphamide: 50-200 mg/day orally

OR

» danazol: 200-800 mg/day orally

OR

» dapsone: 50-100mg/day orally

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OR

» mycophenolate mofetil: 500-2000 mg/day orally

Secondary options

» vincristine: consult specialist for guidance on dose

» In patients who fail treatment with multiple second-line drugs, salvage therapy with an immunosuppressant or immunomodulatory drug may be considered as off-label treatment for immune thrombocytopenia. These include azathioprine, cyclosporine, cyclophosphamide, danazol, dapsone, and mycophenolate. However, evidence supporting their use is lacking.[15] [34]

» Response to mycophenolate may take several weeks, but appears to be durable.[62] [63] [64]

» Vinca alkaloids (e.g., vincristine) can be given in the acute setting only. Despite a high response rate (with a generally rapid response), use is limited by severe side-effects including peripheral neuropathy that may be irreversible.[15] [65]

3rd **low-dose corticosteroid or repeated IVIG infusions**

Primary options

» prednisone: consult specialist for guidance on dose; doses of ≤5 mg/day are recommended

OR

» immune globulin (human): 1 g/kg intravenously as a single dose

» In patients who fail treatment with multiple second-line drugs, salvage therapy with a low-dose corticosteroid or repeated intravenous immune globulin (IVIG) infusions may be considered.

» Low-dose corticosteroids may rarely be considered in responsive patients if they can tolerate corticosteroids and they have no contraindications (e.g., diabetes, hypertension, osteoporosis, peptic ulcer). The minimum effective dosage for the shortest time should be used (optimally not more than 5 mg/day prednisone or equivalent).[15]

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» On-demand, repeated IVIG infusions may be used for responsive patients if tolerated. Most patients respond initially; however, platelet increase is usually transient. There is a need to be vigilant for potential toxicities associated with repeated IVIG infusions, such as renal failure and thrombosis. Hospital attendance as an outpatient is required.

» The treatment goal is to increase platelet count to control clinically relevant bleeding or minimize the risk of major bleeding with minimum toxicity while waiting for spontaneous remission or amelioration.

» Patients should have sufficient platelet levels before undergoing any type of procedure or surgery. Guidelines provide recommendations for target platelet levels.

pregnant: persistent or chronic disease

1st **high-dose methylprednisolone**

Primary options

» methylprednisolone sodium succinate: 1000 mg intravenously every 24 hours for 3 days, followed by treatment with an oral corticosteroid as clinically indicated

» Pregnant patients with immune thrombocytopenia that is unresponsive to initial prednisone or intravenous immune globulin (IVIG) should be treated with high-dose methylprednisolone, usually in combination with IVIG and/or azathioprine.[15] [85]

» Patients should have sufficient platelet levels before undergoing any type of procedure or surgery. Guidelines provide recommendations for target platelet levels.[15] In pregnant women, a target platelet count of ≥50 × 10^3/microliter is recommended for vaginal delivery or cesarean section. For epidural anesthesia, a target platelet count of ≥80 × 10^3/microliter is recommended, although risk is likely to be low in patients with a platelet count of >70 × 10^3/microliter.[87]

adjunct **IVIG and/or azathioprine**

Treatment recommended for SOME patients in selected patient group

Primary options

» immune globulin (human): 1 g/kg intravenously as a single dose, a second

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dose may be given if there is a poor response to initial treatment
-and/or-
» azathioprine: 50-200 mg/day orally

» Patients usually receive intravenous immune globulin (IVIG) and/or azathioprine in addition to high-dose methylprednisolone.

» Azathioprine has been safely used in pregnancy for other indications (e.g., systemic lupus erythematosus or renal transplantation).

» Patients should have sufficient platelet levels before undergoing any type of procedure or surgery. Guidelines provide recommendations for target platelet levels.[15] In pregnant women, a target platelet count of ≥50 × 10^3/microliter is recommended for vaginal delivery or cesarean section. For epidural anesthesia, a target platelet count of ≥80 × 10^3/microliter is recommended, although risk is likely to be low in patients with a platelet count of >70 × 10^3/microliter.[87]

2nd **rituximab**

Primary options

» rituximab: 375 mg/square meter of body surface area intravenously once weekly for 4 doses

» There is limited data on the safe use of rituximab in pregnancy, and there are some concerns about pregnancy outcomes after maternal exposure to rituximab.[86] However, guidelines suggest that rituximab can be considered in pregnancy for very severe cases that have not responded to other treatments.[15] Monitoring is required for immunosuppression and infection. Rituximab is used off-label for immune thrombocytopenia.

2nd **splenectomy**

» Splenectomy is rarely performed in pregnant patients; however, if it is required (e.g., for severe refractory disease) and the patient agrees to the procedure, it is best performed early in the second trimester and may be performed laparoscopically.[15] [20]

» Patients with preoperative platelet counts >20 × 10^3/microliter can safely undergo splenectomy. Prelabour patients with ITP should have sufficient platelet levels. Platelet transfusion may be given to increase platelet count if <20 × 10^3/microliter; however, infusions should be carried

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out with caution as thrombocytosis may occur following splenectomy.

» At least 2 weeks prior to splenectomy, patients should be immunized with vaccines against *S pneumoniae* , *H influenzae* type b, and *N meningitidis* .[67] [68] Local guidance on vaccination pre- and postsplenectomy should be followed.[69] Vaccination may be ineffective for up to 6 months in patients previously treated with rituximab; ideally, vaccinations should be given >6 months before treatment with rituximab or at least 6 months after the final dose.[15] [59] Prophylactic antibiotics should be administered for at least 3 years following splenectomy; some recommend lifelong antibiotic prophylaxis.[67] [70] [71]

Emerging

Rilzabrutinib

Rilzabrutinib is an investigational oral Bruton kinase inhibitor, designed to treat immune-mediated diseases. It has a dual mechanism of action, inhibiting B-cell activation and interrupting antibody-coated cell phagocytosis by Fc gamma receptors in the spleen and liver. It is currently being evaluated in a phase 3 trial comparing rilzabrutinib with placebo in adults and adolescents with persistent or chronic immune thrombocytopenia (ITP).[89] [90] A phase 1 and 2 trial including 60 patients with ITP (median baseline platelet count 15 × 10^3/microliter) who had failed previous treatments (median 4 therapies) showed that 40% of participants achieved a response (platelet count ≥50 × 10^3/microliter) with rilzabrutinib. Median time to response was 11.5 days. No treatment-related bleeding or thrombotic events higher than grade 2 were reported. Common treatment-related adverse events included diarrhea (32% of patients), nausea (30%), and fatigue (10%).[91] The Food and Drug Administration (FDA) has granted fast track designation to this drug for the treatment of ITP.

Efgartigimod alfa

Efgartigimod alfa is a human IgG1-derived Fc fragment, developed to target neonatal Fc receptors to accelerate pathologic IgG degradation in autoimmune disorders. It is currently being evaluated in phase 3 trials for the management of persistent or chronic ITP.[92] In a phase 3 trial of efgartigimod alfa, including 131 patients with chronic ITP, a sustained platelet count response (≥50 × 10^3/microliter for at least 4 of the last 6 weeks) was achieved in 22% of patients compared with 5% receiving a placebo.[93] Efgartigimod alfa was well tolerated, with only mild-to-moderate adverse events. Efgartigimod alfa is currently licensed for the treatment of myasthenia gravis, but not ITP.

Sutimlimab

Sutimlimab is a humanized monoclonal antibody that targets C1s in the classical complement pathway. In a phase 1 trial including 12 patients with chronic or refractory ITP, 5 patients (42%) achieved durable platelet count responses (≥50 × 10^3/microliter in ≥50% of follow-up visits) and 4 achieved complete response (platelet count ≥100 × 10^3/microliter). A response could be maintained in every CR patient by prolonged sutimlimab administration. The median time to response was 2 days. Sutimlimab was generally well tolerated and no patients discontinued treatment due to drug-related adverse events.[94] A phase 2 trial is ongoing.[95] Sutimlimab is currently licensed for the treatment of cold agglutinin disease-associated hemolysis, but not ITP.

Thrombopoietin receptor agonists in pregnancy

Thrombopoietin receptor agonists are not currently recommended in pregnancy, because they are likely to cross the placenta and their safety is not established. However, there is some evidence suggesting that they may have a role in treating severe ITP in pregnant women prior to delivery. A retrospective, observational study including 15 women (17 pregnancies) in women with ITP treated with eltrombopag or romiplostim during pregnancy reported no significant adverse events in the mother or neonate. Initial response to treatment was achieved in 77% of patients.[96] A retrospective review of data from 186 pregnancies in women exposed to romiplostim did not report any specific safety concerns.[97] Multiple case reports support safety (except for the increased risk of neonatal thrombocytosis) and efficacy of thrombopoietin receptor agonists given in the third trimester. Emerging evidence suggests romiplostim may have a role in increasing platelet count to prepare for delivery.[15] [98]

Avatrombopag in children

Avatrombopag (a second-generation oral thrombopoietin receptor agonist) is approved for the treatment of adults with chronic ITP who have had an insufficient response to a previous treatment. The safety and efficacy of avatrombopag in children with ITP who have had an insufficient response to a previous treatment is being evaluated in a phase 3b randomized, placebo-controlled trial.[44] [99]

Secondary prevention

Patients should try to minimize risk of trauma (e.g., by avoiding contact sports and high-risk activities) if platelet count is <50-70 × 10^3/microliter. They should also avoid medications that may affect platelet function (e.g., nonsteroidal anti-inflammatory drugs or aspirin) or coagulation (e.g., warfarin).

Patient discussions

After splenectomy, patients are at higher risk for fatal bacterial infections, at approximately 1 per 1500 patient-years (lower in vaccinated patients).[109] [110] They should be instructed to seek emergency medical treatment in the case of febrile illness.

Pregnant women require routine prenatal care and should be monitored by a team involving a hematologist and gynecologist.

FOLLOW UP

Monitoring

Monitoring

The frequency of platelet count monitoring depends on the severity of thrombocytopenia and is patient and treatment specific.

Complications

Complications	Timeframe	Likelihood
life-threatening bleeding	**short term**	**low**
Spontaneous, life-threatening bleeding is rare, especially in children.[22] Patients with life-threatening bleeding should be treated with the usual medical intensive care strategy. Emergency treatment includes combination therapy with platelet transfusion, intravenous corticosteroids, and intravenous immune globulin.		
intracranial bleeding	**short term**	**low**
Estimated frequency is approximately 0.5% in children and 1.5% in adults.[107] [108]		
complications of long-term thrombopoietin mimetics	**long term**	**medium**
An increased risk of thrombotic events during treatment cannot be ruled out.[46] [105] Patients at high risk of thrombotic events should avoid these agents. Withdrawal thrombocytopenia may occur if treatment is stopped abruptly.[105] Bone marrow biopsy is advised in case of loss of response if adherence is confirmed. Liver function monitoring is required.		
transfusion-transmitted infectious diseases	**variable**	**low**
The risk of a transfusion-transmitted infectious disease from red cell transfusions (if needed secondary to bleeding) are: HIV-1 1:2,000,000; human T-lymphotropic virus type (HTLV)-I/II 1:640,000; hepatitis 1:1,000,000; hepatitis B 1:63,000 to 1:233,000; hepatitis C 1:2,000,000; hepatitis G 1:25 to 1:100.[106] Symptomatic bacterial sepsis risk from transfusion is: RBC 1:500,000; platelets 1:2000 to 1:12,000.		

Prognosis

Most patients will initially respond to standard management with first-line corticosteroids, but additional therapies are required in more than half of cases. In general the prognosis is good, with only 2.5% to 5% of patients being refractory to all available treatments, including splenectomy.[102]

Prognosis is particularly good in children. Children often recover spontaneously within weeks or months, with higher rates of spontaneous remission associated with younger age.[72] Studies report complete remission within 6 months in approximately 70% of children with immune thrombocytopenia.[73] [74]

Mortality is higher in older patients and in those unresponsive to several lines of treatment.[36][103] [104]

Diagnostic guidelines

International

Updated international consensus report on the investigation and management of primary immune thrombocytopenia (http://www.bloodjournal.org/content/115/2/168) [15]

Published by: Journal of the American Society of Hematology **Last published:** 2019

Standardization of terminology, definitions and outcome criteria in immune thrombocytopenic purpura of adults and children (http://www.bloodjournal.org/content/113/11/2386) [1]

Published by: International Working Group of the Vicenza Consensus Conference **Last published:** 2009

Treatment guidelines

International

Updated international consensus report on the investigation and management of primary immune thrombocytopenia (http://www.bloodjournal.org/content/115/2/168) [15]

Published by: Journal of the American Society of Hematology **Last published:** 2019

American Society of Hematology 2019 guidelines for immune thrombocytopenia (https://www.hematology.org/Clinicians/Guidelines-Quality/Guidelines.aspx) [35]

Published by: American Society of Hematology **Last published:** 2019

2013 Clinical practice guide on thrombocytopenia in pregnancy (https://www.hematology.org/Clinicians/Guidelines-Quality/Quick-Reference.aspx) [20]

Published by: American Society of Hematology **Last published:** 2013

Guidelines on the use of intravenous immune globulin for hematologic conditions (https://www.ncbi.nlm.nih.gov/pubmed/17397769) [100]

Published by: National Advisory Committee on Blood and Blood Products of Canada; Canadian Blood Services **Last published:** 2007

Acute childhood idiopathic thrombocytopenia purpura: AIEOP consensus guidelines for diagnosis and treatment (http://www.haematologica.org/content/85/4/420) [101]

Published by: Associazione Italiana di Ematologia e Oncologia **Last published:** 2000

Key articles

- Rodeghiero F, Stasi R, Gernsheimer T, et al. Standardization of terminology, definitions and outcome criteria in immune thrombocytopenic purpura of adults and children: report from an international working group. Blood. 2009 Mar 12;113(11):2386-93. Full text (http://bloodjournal.hematologylibrary.org/cgi/content/full/113/11/2386) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/19005182?tool=bestpractice.bmj.com)

- Provan D, Arnold DM, Bussel JB, et al. Updated international consensus report on the investigation and management of primary immune thrombocytopenia. Blood Adv. 2019 Nov 26;3(22):3780-817. Full text (https://ashpublications.org/bloodadvances/article/3/22/3780/428877/Updated-international-consensus-report-on-the) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/31770441?tool=bestpractice.bmj.com)

- Neunert C, Terrell DR, Arnold DM, et al. American Society of Hematology 2019 guidelines for immune thrombocytopenia. Blood Adv. 2019 Dec 10;3(23):3829-66. Full text (https://ashpublications.org/bloodadvances/article/3/23/3829/429213/American-Society-of-Hematology-2019-guidelines-for) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/31794604?tool=bestpractice.bmj.com)

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full/10.1111/j.1365-2141.2009.07615.x) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/19245432?tool=bestpractice.bmj.com)

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Figure 1 – BMJ Best Practice Numeral Style

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