Immune Thrombocytopenic Purpura (ITP) Treatment & Management

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Practice Essentials

Immune thrombocytopenic purpura (ITP) is a clinical syndrome in which a decreased number of circulating platelets (thrombocytopenia) (see the image below) manifests as a bleeding tendency, easy bruising (purpura), or extravasation of blood from capillaries into skin and mucous membranes (petechiae). Although most cases of acute ITP, particularly in children, are mild and self-limited, intracranial hemorrhage may occur when the platelet count drops below 10 × 10⁹/L (< 10 × 10³/µL);¹ this occurs in 0.5-1% of children, and half of these cases are fatal.²

![Peripheral blood smear from a patient with immune thrombocytopenic purpura (ITP) shows a decreased number of platelets, a normal-appearing neutrophil, and normal-appearing erythrocytes. ITP is diagnosed by excluding other diseases; therefore, the absence of other findings from the peripheral smear is at least as important as the observed findings. This smear demonstrates the absence of immature leukocytes (as in leukemia) and fragmented erythrocytes (as in thrombotic thrombocytopenic purpura) and no clumps of platelets (as in pseudothrombocytopenia).](image)

Signs and Symptoms

ITP is a primary illness occurring in an otherwise healthy person. Signs of chronic disease, infection, wasting, or poor nutrition indicate that the patient has another illness. Splenomegaly excludes the diagnosis of ITP.
An initial impression of the severity of ITP is formed by examining the skin and mucous membranes, as follows:

- Widespread petechiae and ecchymoses, oozing from a venipuncture site, gingival bleeding, and hemorrhagic bullae indicate that the patient is at risk for a serious bleeding complication.
- If the patient's blood pressure was taken recently, petechiae may be observed under and distal to the area where the cuff was placed and inflated.
- Suction-type electrocardiograph (ECG) leads may induce petechiae.
- Petechiae over the ankles in ambulatory patients or on the back in bedridden ones suggest mild thrombocytopenia and a relatively low risk for a serious bleeding complication.

Findings suggestive of intracranial hemorrhage include the following:

- Headache, blurred vision, somnolence, or loss of consciousness.
- Hypertension and bradycardia, which may be signs of increased intracranial pressure.
- On neurologic examination, any asymmetrical finding of recent onset.
- On fundoscopic examination, blurring of the optic disc margins or retinal hemorrhage.

See Clinical Presentation for more detail.

**Diagnosis**

On complete blood cell count, isolated thrombocytopenia is the hallmark of ITP. Anemia and/or neutropenia may indicate other diseases. Findings on peripheral blood smear are as follows:

- The morphology of red blood cells (RBCs) and leukocytes is normal.
- The morphology of platelets is typically normal, with varying numbers of large platelets.
- If most of the platelets are large, approximating the diameter of red blood cells, or if they lack granules or have an abnormal color, consider an inherited platelet disorder.

Many children with acute ITP have an increased number of normal or atypical lymphocytes on the peripheral smear, reflecting a recent viral illness. Clumps of platelets on a peripheral smear prepared from ethylenediaminetetraacetic acid (EDTA)–anticoagulated blood are evidence of pseudothrombocytopenia. This diagnosis is established if the platelet count is normal when repeated on a sample from heparin-anticoagulated or citrate-anticoagulated blood.

Aspects of bone marrow aspiration and biopsy are as follows:

- The value of bone marrow evaluation for a diagnosis of ITP is unresolved.
- Biopsy in patients with ITP shows a normal-to-increased number of megakaryocytes in the absence of other significant abnormalities.
- In children, bone marrow examination is not required except in patients with atypical hematologic findings, such as immature cells on the peripheral smear or persistent neutropenia.
- In adults older than 60 years, biopsy is used to exclude myelodysplastic syndrome or leukemia.
- In adults whose treatment includes corticosteroids, a baseline pretreatment biopsy may prove useful for future reference, as corticosteroids can change marrow morphology.
Biopsy is performed before splenectomy to evaluate for possible hypoplasia or fibrosis. Unresponsiveness to standard treatment after 6 months is an indication for bone marrow aspiration.

See Workup for more detail.

Management

ITP has no cure, and relapses may occur years after seemingly successful medical or surgical management. Most children with acute ITP do not require treatment, and the condition resolves spontaneously.[7,8]

Treatment is as follows:

- Corticosteroids remain the drugs of choice for the initial management of acute ITP
- Oral prednisone, IV methylprednisolone, or high-dose dexamethasone may be used [9,10,11]
- IV immunoglobulin (IVIG) has been the drug of second choice for many years [12,13]
- For Rh(D)-positive patients with intact spleens, IV Rho immunoglobulin (RhIG) offers comparable efficacy, less toxicity, greater ease of administration, and a lower cost than IVIG [14,15]
- RhIG can induce immune hemolysis (immune hemolytic anemia) in Rh(D)-positive persons and should not be used when the hemoglobin concentration is less than 8 g/dL
- Sporadic cases of massive intravascular hemolysis, disseminated intravascular coagulation (particularly in elderly individuals), and renal failure have been reported with RhIG
- Rituximab is third-line therapy
- Platelet transfusions may be required to control clinically significant bleeding but are not recommended for prophylaxis
- If 6 months of medical management fails to increase the platelet count to a safe range (about 30,000/µL), splenectomy becomes an option
- Thrombopoietin receptor agonists (ie, eltrombopag, romiplostim) may maintain platelet counts at safe levels in adults with chronic ITP refractory to conventional medical management or splenectomy

Pregnant women require special consideration for delivery, as follows:[18]:

- If the platelet count is greater than 50 × 10^9/L (>50 × 10^3/µL), the risk of serious hemorrhage is low, but beginning oral prednisone a week before delivery is a reasonable precaution
- If the platelet count is less than 50 × 10^9/L (50 × 10^3/µL) before delivery, treatment with oral prednisone and IVIG is recommended
- Avoiding the use of IV RhIG in this situation until safety data are available is advisable
- Rarely, splenectomy may be required to manage acute hemorrhage [19]

See Treatment and Medication for more detail.

Background

Immune thrombocytopenic purpura (ITP)—also known as idiopathic thrombocytopenic purpura and, more recently, as immune thrombocytopenia—is a clinical syndrome in which a decreased
number of circulating platelets (thrombocytopenia) manifests as a bleeding tendency, easy bruising (purpura), or extravasation of blood from capillaries into skin and mucous membranes (petechiae).

In persons with ITP, platelets are coated with autoantibodies to platelet membrane antigens, resulting in splenic sequestration and phagocytosis by mononuclear macrophages. The resulting shortened life span of platelets in the circulation, together with incomplete compensation by increased platelet production by bone marrow megakaryocytes, results in a decreased platelet count.

Peripheral blood smear from a patient with immune thrombocytopenic purpura (ITP) shows a decreased number of platelets, a normal-appearing neutrophil, and normal-appearing erythrocytes. ITP is diagnosed by excluding other diseases; therefore, the absence of other findings from the peripheral smear is at least as important as the observed findings. This smear demonstrates the absence of immature leukocytes (as in leukemia) and fragmented erythrocytes (as in thrombotic thrombocytopenic purpura) and no clumps of platelets (as in pseudothrombocytopenia).

No single laboratory result or clinical finding establishes a diagnosis of ITP; it is a diagnosis of exclusion. The differential diagnosis includes such other causes of thrombocytopenia as leukemia, myelophthisic marrow infiltration, myelodysplasia, aplastic anemia, and adverse drug reactions. Pseudothrombocytopenia due to platelet clumping is also a diagnostic consideration.

For discussion of ITP in pregnancy, see Immune Thrombocytopenia and Pregnancy. For patient education information, see the First Aid and Injuries Center, as well as Bruises.

Pathophysiology

In immune thrombocytopenic purpura (ITP), an abnormal autoantibody, usually immunoglobulin G (IgG) with specificity for one or more platelet membrane glycoproteins (GPs), binds to circulating platelet membranes. [20, 21, 22]
Autoantibody-coated platelets induce Fc receptor-mediated phagocytosis by mononuclear macrophages, primarily but not exclusively in the spleen. The spleen is the key organ in the pathophysiology of ITP, not only because platelet autoantibodies are formed in the white pulp, but also because mononuclear macrophages in the red pulp destroy immunoglobulin-coated platelets.

If bone marrow megakaryocytes cannot increase production and maintain a normal number of circulating platelets, thrombocytopenia and purpura develop. Impaired thrombopoiesis is attributed to failure of a compensatory increase in thrombopoietin and megakaryocyte apoptosis.

**Etiology**

In children, most cases of immune thrombocytopenic purpura (ITP) are acute, manifesting a few weeks after a viral illness. In adults, most cases of ITP are chronic, manifesting with an insidious onset, and occur in middle-aged women. These clinical presentations suggest that the triggering events may be different. However, in both children and adults, the cause of thrombocytopenia (destruction of antibody-coated platelets by mononuclear macrophages) appears to be similar.

**Autoantibody stimulation**

See the list below:

- In chronic ITP, for unknown reasons, membrane glycoproteins (GPs) on the surface of platelets become immunogenic, stimulating the production of platelet autoantibodies
- In acute ITP, the stimulus for autoantibody production is also unknown; platelet membrane cryptantigens may become exposed by the stress of infection, or pseudoantigens may be formed by the passive adsorption of pathogens on platelet surfaces

**Autoantibody specificity**

See the list below:

- In persons with chronic ITP, approximately 75% of autoantibodies are directed against platelet GPIIb/IIIa or GPIb/IX GP complexes
- Presumably, the remaining 25% are directed against other membrane epitopes, including GPV, GPIa/IIa, or GPIV

**Role of the spleen**

- The spleen is the site of autoantibody production (white pulp)
- It is also the site of phagocytosis of autoantibody-coated platelets (red pulp)
- The slow passage of platelets through splenic sinusoids with a high local concentration of antibodies and Fc-gamma receptors on splenic macrophages lend to the uniqueness of the spleen as a site of platelet destruction
- Low-affinity macrophage receptors, Fc gamma RIIA, and Fc gamma RIIIA bind immune-complexed IgG and are the key mediators of platelet clearance
Platelet destruction

See the list below:

- The mononuclear macrophage system of the spleen is responsible for removing platelets in ITP, as demonstrated by the fact that splenectomy results in prompt restoration of normal platelet counts in most patients with ITP.
- Platelets are sequestered and destroyed by mononuclear macrophages, which are neither reticular nor endothelial in origin. Therefore, the former designation of reticuloendothelial system is considered imprecise.
- Immune destruction of immunoglobulin-coated platelets is mediated by macrophage IgG Fc (Fc gamma RI, Fc gamma RII, and Fc gamma RIII) and complement receptors (CR1, CR3).

Epidemiology

United States

The annual incidence of immune thrombocytopenic purpura (ITP) is estimated to be five cases per 100,000 children and two cases per 100,000 adults, but these data are not from large population-based studies. Most cases of acute ITP, particularly in children, are mild and self-limited and may not receive medical attention. Therefore, estimated incidences of ITP are difficult to determine and are likely to understate the full extent of the disease. The age-adjusted prevalence of ITP in Maryland was reported as 9.5 per 100,000 persons by Segal and Powe.

International

A French study reported an incidence of ITP of 2.9 cases per 100,000 person-years, with peaks in children and in those older than 60 years of age and a higher frequency of ITP in males in these subgroups. ITP showed seasonal variation, with a peak in winter and a nadir in summer. Persistence or chronicity occurred in 36% of children compared with 67% of adults. In adults, 18% of ITP cases were secondary, with malignancy the main cause.

Mortality/Morbidity

The primary cause of long-term morbidity and mortality in patients with immune thrombocytopenic purpura (ITP) is hemorrhage. Spontaneous or accidental trauma–induced intracranial hemorrhage is the most frequent cause of death in association with ITP. Most cases of intracranial hemorrhage occur in patients whose platelet counts are less than $10 \times 10^9$/L ($<10 \times 10^3$/µL). This situation occurs in 0.5-1% of cases in children, and half of those are fatal. In one study, 17% of children experienced a major hemorrhage. The estimated frequency of intracranial hemorrhage in adults with ITP is 1.5%.

Treatment-related morbidity may result from the need to maintain the platelet count in a safe range in patients with chronic treatment-resistant ITP. These patients may require a long-term course of corticosteroids, other immunosuppressive medications, or splenectomy, and thus may experience complications of therapy with corticosteroids or splenectomy.
Sex- and Age-related Demographics

In children, ITP is more common in boys than in girls. In middle-aged adults, women are affected more frequently than men. \[1\]

Children may develop ITP at any age, but the incidence peaks in children aged 1-6 years. \[1\]
Adults may be affected at any age, but most cases are diagnosed in women aged 30-40 years.

Onset in a patient older than 60 years is uncommon, and a search for other causes of thrombocytopenia is warranted. The most likely causes in these persons are myelodysplastic syndromes, acute leukemia, and marrow infiltration (myelophthisis). Persons with ITP who are 70 years or older are at increased risk for spontaneous bleeding and treatment-related adverse events. \[3\]

Prognosis

Prognosis varies in children and adults.

Children

More than 80% of children with untreated immune thrombocytopenic purpura (ITP) have a spontaneous recovery with completely normal platelet counts in 2-8 weeks. Fatal bleeding occurs in 0.9% upon initial presentation.

A systematic review and meta-analysis identified the following factors associated with higher risk of ITP in children becoming chronic: \[32\]:

- Female gender (odds ratio [OR] 1.17)
- Age ≥11 years at presentation (OR 2.47)
- No preceding infection or vaccination (OR 3.08)
- Insidious onset (OR 11.27)
- Platelet count ≥20 × 10^9/L at presentation OR 2.15)
- Presence of antinuclear antibodies (OR 2.87)
- Treatment with methylprednisolone plus intravenous immunoglobulin (OR 2.67)

Factors associated with lower likelihood of developing chronic ITP were as follows:

- Mucosal bleeding at diagnosis (OR 0.39)
- Treatment with intravenous immunoglobulin alone (OR 0.71)

Adults

Approximately 60-90% of adults with ITP respond with an increased platelet count after treatment with prednisone or prednisone and IV RhIG or IVIG. Of those adults who do not maintain an increased platelet count and who require splenectomy, approximately two thirds have a sustained response and 10-15% have a partial response. \[1, 3\]
History

The medical history in a patient with a clinical suspicion of immune thrombocytopenic purpura (ITP) should focus on the following:

- Factors that suggest another disease for which thrombocytopenia is a complication
- Signs and symptoms that differentiate mild, moderate, and severe bleeding tendencies

Other systemic illnesses

Considerations include the following:

- In adults, thrombocytopenic purpura may be a manifestation of systemic lupus erythematosus [34] or acute or chronic leukemia
- Thrombocytopenic purpura may be a manifestation of a myelodysplastic syndrome, particularly in patients older than 60 years
- In young children, ITP may manifest as a primary immune deficiency syndrome

Postviral illness

In children, most cases of ITP are acute, and onset seems to occur within a few weeks of recovery from a viral illness. The severity of symptoms of the viral illness does not correlate with the degree of thrombocytopenia.

Thrombocytopenia is a recognized complication after infection with Epstein-Barr virus, varicella virus, cytomegalovirus, rubella virus, or hepatitis virus (A, B, or C). However, the most typical association is with a vaguely defined viral upper respiratory infection or gastroenteritis.

Transient thrombocytopenia has been reported to be associated with recent immunization with attenuated live-virus vaccines. [35, 36]

Human immunodeficiency virus (HIV) infection

In persons infected with HIV, thrombocytopenia may occur during the acute retroviral syndrome coincident with fever, rash, and sore throat. However, thrombocytopenia may also be a manifestation of acquired immunodeficiency syndrome (AIDS), occurring late in the course of HIV infection. HIV-related thrombocytopenia is particularly likely to occur in people who abuse drugs.

Drug-induced thrombocytopenia

Regard any medication taken by a person who develops thrombocytopenia as a potential causative agent. A history of all prescription and over-the-counter medications is required to exclude drug-related thrombocytopenia. [37]
More than 1444 currently approved drugs are listed in the US Food and Drug Administration's Adverse Event Reporting System (AERS) database, all of which have been suspected of causing clinical episodes of thrombocytopenia. However, only 573 of these agents have a statistically significant reporting association with thrombocytopenia and of these, perhaps only two dozen satisfy clinical and laboratory criteria for evidence of causality for drug-induced thrombocytopenia.

For a diagnosis of drug-induced thrombocytopenia to be made with confidence, the development of the low platelet count should exhibit a strict temporal relationship with the initiation of the medication; the platelet count should recover when the offending medication is discontinued; the likelihood of drug-induced thrombocytopenia should be greater than any other plausible cause; and ideally, in vitro evidence of drug-dependent antibody formation should exist. Reese et al have published a useful online database of the drugs most likely to cause thrombocytopenia.[38]

Persons who have been sensitized (by previous exposure) to quinidine or quinine may develop immune-mediated drug purpura within hours to days of subsequent exposure. To exclude drug purpura in a person previously treated with quinidine or quinine, the history must include questions about possible exposure to over-the-counter medications, tonic water in cocktails, or bitter lemon beverages.

Investigate the records of patients who have been hospitalized and who develop acute thrombocytopenias for all of their medications that are listed and not listed in nursing charts. For example, patients who are at risk for heparin-induced thrombocytopenia because of current or recent treatment with heparin may be receiving the heparin with the routine flushing of intravenous (IV) catheters, and this exposure may not be listed on the nursing medication sheet. Many catheters are also heparin impregnated, and unless checked, they can be a hidden cause of heparin-induced thrombocytopenia.

Antiplatelet drugs that are glycoprotein IIb/IIIa (GPIIb/IIIa) Inhibitors may result in ITP. These include eptifibatide (Integrilin), and abciximab (ReoPro), which is a Fab fragment of the chimeric human-murine monoclonal antibody 7E3 directed against the platelet GPIIb/IIIa receptor.

Other drugs associated with drug purpura include the following:

- Antibiotics (eg, cephalosporins, rifampicin)
- Gold salts
- Analgesics
- Neuroleptics
- Diuretics
- Antihypertensives

Acute and chronic alcohol consumption may also be associated with thrombocytopenia. In persons with chronic liver disease, hypersplenism with secondary thrombocytopenia is not uncommon.
Bleeding tendency

See the list below:

- Determine the extent and duration of the bleeding tendency to estimate the severity of the illness and the potential risk for a serious hemorrhage. Previous surgical history can often provide a useful clue regarding the acuteness of thrombocytopenia.
- Query patients to elicit signs or symptoms of intracranial bleeding, such as headache, blurred vision, somnolence, or loss of consciousness.
- Ask about any recent accidental head trauma.
- Record any bleeding, including petechiae, ecchymoses, epistaxis, menorrhagia, melena, or hematuria. Determine whether bruising or bleeding is a recurrent problem.

Physical

Like the medical history, the physical examination should focus on the following:

- Findings that suggest another disease for which thrombocytopenia is a complication
- Physical signs that suggest serious internal bleeding

General health

See the list below:

- Immune thrombocyticopenic purpura (ITP) is a primary illness occurring in an otherwise healthy person
- Signs of chronic disease, infection, wasting, or poor nutrition indicate that the patient has another illness
- Vital signs: Hypertension and bradycardia may be signs of increased intracranial pressure and evidence of an undiagnosed intracranial hemorrhage.

Skin and mucous membranes

See the list below:

- An initial impression of the severity of ITP is formed by examining the skin and mucous membranes.
- Widespread petechiae and ecchymoses, oozing from a venipuncture site, gingival bleeding, and hemorrhagic bullae indicate that the patient is at risk for a serious bleeding complication. If the patient’s blood pressure was taken recently, petechiae may be observed under and distal to the area where the cuff was placed and inflated. Suction-type electrocardiograph (ECG) leads may similarly induce petechiae.
- Mild thrombocytopenia and a relatively low risk for a serious bleeding complication may manifest as petechiae over the ankles in patients who are ambulatory or on the back in patients who are bedridden.
Other organ systems

On cardiovascular examination, distant low-amplitude heart sounds accompanied by jugular venous distention may be evidence of hemopericardium.

On abdominal examination, in children with acute ITP the presence of a readily palpable spleen is not typical. In an adult, hepatosplenomegaly is also atypical for ITP and may indicate chronic liver and other diseases; in fact, splenomegaly excludes the diagnosis of ITP.

Nervous system

- Any asymmetrical finding of recent onset can indicate an intracranial hemorrhage
- Pupils should be equal in size and patients should have intact extraocular muscles and symmetrical eye movements
- Balance and gait should be intact
- Funduscopic examination reveals whether the margins of the optic disc are blurred; examine the patient for the presence of retinal hemorrhages and other evidence of increased intracranial pressure

Laboratory Studies

The workup for immune thrombocytopenic purpura (ITP) starts with a complete blood cell (CBC) count. The hallmark of ITP is isolated thrombocytopenia; anemia and/or neutropenia may indicate other diseases.

On peripheral blood smear, the morphology of red blood cells (RBCs) and leukocytes is normal. The morphology of platelets is typically normal, with varying numbers of large platelets. Some persons with acute ITP may have megathrombocytes or stress platelets, reflecting the early release of megakaryocytic fragments into the circulation. If most of the platelets are large, approximating the diameter of RBCs, or if they lack granules or have an abnormal color, consider an inherited platelet disorder.

Clumps of platelets on a peripheral smear prepared from ethylenediaminetetraacetic acid (EDTA)–anticoagulated blood are evidence of pseudothrombocytopenia. The diagnosis of this type of pseudothrombocytopenia is established if the platelet count is normal when repeated on a sample from heparin-anticoagulated or citrate-anticoagulated blood.

In patients who have risk factors for HIV infection, a blood sample should be tested with an enzyme immunoassay for anti-HIV antibodies. During the acute HIV retroviral syndrome, the results of the anti-HIV assay may be negative. In this situation, a polymerase chain reaction for HIV DNA is more reliable than the anti-HIV assay.

In selected women, the medical history may suggest a chronic, recurrent, multisystemic illness with vague, generalized signs or symptoms, such as recurrent, multiple, painful, tender, or swollen joints. In such cases, a negative antinuclear antibody (ANA) result is useful in diagnosing ITP if the patient's thrombocytopenia becomes chronic and resistant to treatment.
If anemia and thrombocytopenia are present, a positive direct antiglobulin (Coombs) test result may help establish a diagnosis of Evans syndrome.

In children with ITP who have already received their first dose of measles-mumps-rubella (MMR) vaccine, the American Society of Hematology recommends measuring vaccine titers. If the titers indicate full immunity (as is the case in up to 95% of children), then no further MMR vaccine should be given. If the titers indicate inadequate immunity, the child should receive further immunization with MMR vaccine at the recommended age.[8]

Assays for platelet antigen–specific antibodies, platelet-associated immunoglobulin, or other antiplatelet antibodies are available in some medical centers and certain mail-in reference laboratories. The reliability of the results of a platelet antibody test is highly specific to the laboratory used. A negative antiplatelet antibody assay result does not exclude the diagnosis of ITP.[40] The authors do not recommend this test as part of the routine evaluation. Testing for antiplatelet antibodies is not required to diagnose ITP.

Studies from Italy,[41, 42] Japan,[43, 44] and Korea[45] indicate that many persons with ITP have Helicobacter pylori gastric infections and that eradication of H pylori results in increased platelet counts. In the United States and Spain, however, the prevalence of H pylori infections does not appear to be increased in persons with ITP, and eradication of H pylori has not increased platelet counts.[46, 47] Therefore, routine testing for H pylori infections in adults and children with ITP is not recommended.

Imaging Studies

Computed tomography (CT) scanning and magnetic resonance imaging (MRI) are relatively benign and useful noninvasive imaging studies that can be used to rule out other causes of thrombocytopenia. However, they are not part of the routine evaluation of patients who may have immune thrombocytopenic purpura (ITP). However, prompt CT scanning or MRI is indicated when the medical history or physical findings suggest serious internal bleeding.

Histologic Findings

Bone marrow aspirate

The cellularity of the aspirate and the morphology of erythroid and myeloid precursors should be normal. The number of megakaryocytes may be increased. Because the peripheral destruction of platelets is increased, megakaryocytes may be large and immature, although in many cases the megakaryocyte morphology is normal. Older patients require a careful examination of megakaryocyte morphology to exclude an early myelodysplastic syndrome.

Bone marrow biopsy

Sections of a needle biopsy specimen or marrow clot should reveal normal marrow cellularity, without evidence of hypoplasia or increased fibrosis.
Splenic evaluation

The spleen reveals no specific findings. In adults, the microscopic finding of extramedullary hematopoiesis is atypical and indicates myeloid metaplasia. Spleens removed from patients with immune thrombocytopenic purpura (ITP) should be carefully examined for a primary splenic lymphoma or granuloma or other signs of an undiagnosed infectious disease.

Bone Marrow Examination

**Bone marrow aspiration and biopsy** in patients with immune thrombocytopenic purpura (ITP) demonstrates a normal-to-increased number of megakaryocytes in the absence of other significant abnormalities. The value of bone marrow evaluation for a diagnosis of ITP is unresolved, and more data are needed to establish clear guidelines.\[4\]

Recommendations for adult patients are as follows:

- In adults who are thrombocytopenic and older than 60 years, we examine the bone marrow to exclude myelodysplastic syndrome or leukemia
- In adults whose treatment includes corticosteroids, baseline pretreatment bone marrow aspiration may be useful for future reference. Many adults have treatment-resistant chronic ITP evident after 3-6 months of treatment, and an alternative diagnosis may be pursued vigorously at that time. Marrow aspirate obtained before any steroid-induced changes may have occurred can be useful.
- Perform bone marrow aspiration and biopsy to evaluate for possible hypoplasia or fibrosis before splenectomy is performed

American Society of Hematology guidelines advise that bone marrow examination is not necessary in children and adolescents with the typical features of ITP, or in children who fail IVIg therapy. The guidelines suggest that bone marrow examination is also not necessary in similar patients before initiation of treatment with corticosteroids or before splenectomy.\[8\]

Bone marrow examination is indicated in children with atypical hematologic findings, such as immature cells on the peripheral smear or persistent neutropenia.\[5\] Many children with acute ITP have an increased number of normal or atypical lymphocytes on the peripheral smear, reflecting a recent viral illness. Unresponsiveness to standard treatment after 6 months is an indication for bone marrow aspiration.

Medical Care

The goal of medical care for immune thrombocytopenic purpura (ITP) is to increase the platelet count to a safe level, permitting patients to live normal lives while awaiting spontaneous or treatment-induced remission. ITP has no cure, and relapses may occur years after seemingly successful medical or surgical management.\[6\]
Although the paradigm may be shifting somewhat with the expanding experience with thrombopoietin receptor analogs in chronic ITP, the long-term consequences associated with their use remain to be established and the delayed platelet count responses these agents produce are not conducive to preventing or reversing the potential of acute bleeding complications in newly diagnosed ITP. Therefore, for now, corticosteroids (ie, oral prednisone, intravenous [IV] methylprednisolone, or high-dose dexamethasone) should remain the drugs of choice for the initial management of acute ITP. Treatment with corticosteroids may not only reduce the rate of platelet destruction but may also rapidly alter endothelial cell integrity to facilitate primary hemostasis and to reduce bleeding and bruising.

Because corticosteroid administration may change marrow morphology, performance of a bone marrow aspiration and biopsy should be considered to confirm the diagnosis of ITP if the clinical presentation, patient age, or other findings are atypical for acute ITP before the patient is treated with corticosteroids.

IV immunoglobulin (IVIG) has been the drug of second choice (after corticosteroids) for many years. However, for Rh(D)-positive patients with ITP and intact spleens, IV Rho immunoglobulin (RhIG) offers comparable efficacy, less toxicity, greater ease of administration, and a lower cost than IVIG.

The limitation of using IV RhIG is the lack of efficacy in Rh(D)-negative or splenectomized patients. Also, IV RhIG may induce immune hemolysis (immune hemolytic anemia) in Rh(D)-positive persons, which is the most common adverse effect, and should not be used when the hemoglobin concentration is less than 8 g/dL. Sporadic cases of massive intravascular hemolysis—disseminated intravascular coagulation (particularly in elderly individuals), and renal failure—have been reported.

Treatment in children

Most children with acute ITP do not require treatment, and thrombocytopenia resolves spontaneously. The American Society of Hematology (ASH) recommends that children who have no bleeding or mild bleeding (eg, cutaneous manifestations such as bruising and petechiae) be managed with observation alone regardless of platelet count. A retrospective review by Schultz et al found that this approach did not lead to an increase in later treatment or an increase in delayed bleeding symptoms.

For pediatric patients requiring treatment, the ASH recommends a single dose of IVIg (0.8 to 1 g/kg) if a more rapid increase in the platelet count is desired, or a short course of corticosteroids, as first-line treatment.

The ASH notes the significant risk of hemolysis with IV Rh,D immune globulin (RhIG, anti-D immune), and advises against its use in children with a hemoglobin concentration that is decreased because of bleeding, or in those with evidence of autoimmune hemolysis. However, the ASH suggests that a single dose of IV RhIG can be used as first-line treatment in Rh-positive, nonsplenectomized children with a negative direct antiglobulin test (DAT) who require treatment.
An advantage of IV RhIG is that if bone marrow aspiration is unacceptable to parents and if the diagnosis of acute ITP is equivocal, IV RhIG is an effective treatment that avoids the problem of a misdiagnosis of acute leukemia because of steroid-related changes in the marrow.

For children or adolescents with ITP who have significant ongoing bleeding despite treatment with IVIG, RhIG, or conventional doses of corticosteroids, the ASH recommends considering rituximab or high-dose dexamethasone for second-line treatment. Rituximab or high-dose dexamethasone may also be considered as an alternative to splenectomy or as treatment for children and adolescents who do not respond favorably to splenectomy.[8]

Treatment in adults

In adults, treatment is recommended for a platelet count <30×10⁹/L. The ASH recommends that if treatment is needed and corticosteroids are given, longer courses (eg, prednisone 1 mg/kg orally for 21 days then tapered) are preferred over shorter courses of corticosteroids or IVIG as first-line treatment. IVIG be used with corticosteroids in patients who require a more rapid increase in platelet count. If corticosteroids are contraindicated, either IVIG (initially, 1 g/kg in a single dose) or IV RhIG (in appropriate patients) may be used as a first-line treatment.[8]

The ASH suggests consideration of thrombopoietin receptor agonists for patients at risk of bleeding when splenectomy is contraindicated and at least one other therapy has failed, and recommends thrombopoietin receptor agonists in adult patients who relapse after splenectomy and are at risk for bleeding. The ASH suggests consideration of rituximab in patients at risk of bleeding when one line of therapy (eg, corticosteroids, IVIg, splenectomy) has failed.[8]

Additional precautions are required for patients with hypertension, peptic ulcers, recent aspirin ingestion, or other risk factors for increased bleeding. Considerations are as follows:

- Aspirin inhibits platelet function by acetylating platelet cyclooxygenase, increasing the risk of bleeding because it adds a platelet functional defect to the quantitative defect already present from the severe thrombocytopenia. In addition, platelet dysfunction may be induced by the platelet antibody, which is potentiated by the superimposition of the aspirin-platelet defect. Because of this effect, aspirin is contraindicated in persons with ITP.
- Adults whose platelet counts are greater than (50 × 10⁹/L (>50 × 10³/µL) typically have minimal purpura, and the risk of a severe hemorrhage is low. They may be treated without a specific medication.
- Platelet transfusions may be required to control clinically significant bleeding but are not recommended for prophylaxis. Transfused platelets also have decreased circulation, and repeated platelet transfusions may lead to platelet alloimmunization.

Treatment in pregnant women

Pregnant women with no bleeding manifestations whose platelet counts are 30 × 10⁹/L or higher do not require any treatment until 36 weeks' gestation, unless delivery is imminent. For pregnant women with platelet counts below 30 × 10⁹/L, or clinically relevant bleeding, first-line therapy is oral corticosteroids or IVIG. Oral prednisone and prednisolone cross the placenta less readily.
than dexamethasone. Although ASH guidelines recommend a starting dose of prednisone of 1mg/kg daily, other experts recommend a starting dose of 0.25 to 0.5 mg/kg, as there is no evidence that a higher starting dose is better. The recommended starting dose of IVIG is 1 g/kg.[18]

Refractory ITP in pregnancy can be treated with corticosteroids and IVIG in combination, or splenectomy (in the second trimester).[18] Rarely, splenectomy may be required to manage acute hemorrhage.[19]

Azathioprine and RhIG are relatively contraindicated in pregnancy. The standard dose of IV RhIG for ITP contains approximately 10-fold the concentration of anti-D that is in the standard antepartum dose of intramuscular RhIG for Rh immunoprophylaxis. Other third-line agents that are not recommended in pregnancy, but whose use in this setting has been described, include the following agents (all of them pregnancy category C)[18]:

- Cyclosporine
- Dapsone
- Thrombopoietin receptor agonists
- Alemtuzumab
- Rituximab

For more information, see Immune Thrombocytopenia and Pregnancy.

**Thrombopoietin receptor agonists**

For many years, the only treatment options after corticosteroids, IV RhIG, IVIG, and rituximab were cyclophosphamide, azathioprine, and danazol. Interventions with decreased certain efficacy and with conflicting reports in the literature include alemtuzumab, azathioprine, danazol, dapsone, vincristine, ascorbic acid, colchicine, and interferon alfa.[49, 50, 51, 52, 53, 54, 55]

In 2008, two thrombopoietin receptor agonists, romiplostin (*Nplate*) and eltrombopag (*Promacta*), became available for patients with chronic ITP. In August 2015, the U.S. Food and Drug Administration expanded the indication for eltrombopag to include treatment of chronic ITP in patients 1 year of age and older who have not achieved an appropriate response with other medical therapy or splenectomy.[56]

The limited clinical experiences with these agents are promising. However, the ultimate efficacy and safety of these new agents will not be fully evaluable until data on larger numbers of patients become available.

In one prospective, randomized controlled study comparing romiplostin with the standard of care for the treatment of chronic ITP, romiplostim administration was associated with higher rates of platelet count responses, decreased need for splenectomy, fewer episodes of serious bleeding and blood transfusions, and decreased need for initiating additional medical treatments. Romiplostim therapy was also associated with improved quality of life.[57] In a study of long-term romiplostim
treatment, a small cohort of children with severe chronic ITP increased and maintained platelet counts for over 4 years, with good tolerability and without significant toxicity.[58]

A systematic review concluded that romiplostim is effective and generally well tolerated in patients 65 years of age and older with ITP. Complications included nonsignificant trends toward increased risks of grade ≥3 bleeding and thromboembolic events.[59]

Eltrombopag was studied in a phase III double-blind trial in adults with previously treated ITP lasting more than 6 months and with platelet counts lower than 30,000/µL. Patients received treatment with local standard care plus eltrombopag (50 mg) or placebo for 6 months.[60]

Of 196 patients in the study, 106 (79%) patients in the eltrombopag group responded to treatment at least once, compared with 17 (28%) in the placebo group. Toxic reactions in the eltrombopag group included thromboembolic events (2%), mild increases in alanine aminotransferase levels (3%), and increased total bilirubin levels (4%).[60]

Surgical Care

In persons with acute immune thrombocytopenic purpura (ITP), splenectomy usually results in rapid, complete, and life-long clinical remission.

In persons with chronic ITP, the results of splenectomy are typically less predictable than they are in patients with acute ITP. Platelet counts may not fully revert to normal values, and relapses are not uncommon after 5 years.

Laparoscopic splenectomy is an interventional approach that is less invasive than traditional splenectomy and offers the promise of decreased postoperative morbidity and shorter recovery.[61, 62] However, the ultimate role for laparoscopic splenectomy in ITP depends on long-term follow-up to determine whether this approach is as effective as conventional splenectomy for visual scrutiny of the abdominal cavity to identify accessory spleens.

Splenectomy results in a lifelong increased risk of sepsis from infection by encapsulated bacteria[63, 64, 65] and Babesia, as follows[66]:

- In adults, this risk is estimated to be approximately 1%, with a fatal outcome in approximately 1 per 1500 patient-years.
- In children, the risk of bacterial sepsis after splenectomy is estimated to be 1-2%. Many pediatricians recommend delaying splenectomy until children are 5 years of age.
- These estimates are presumably based on early data and may be inflated, given the increased alertness to the importance of early treatment, availability of more effective antibiotics, and availability of vaccines against specific encapsulated bacteria.
- Before one concludes that medical management and splenectomy have failed and that treatment with alternative options is needed, perform an imaging study to ensure that the problem is not associated with an accessory spleen.
- Recent studies suggest that the initiation of thrombopoietin mimetics may obviate splenectomy in a significant number of individuals with chronic ITP.
In addition, splenectomy has been associated in adults with an increased incidence of venous and arterial thrombosis,[67] a twofold increase in deaths from cardiovascular disease,[68] and an increased rate of pulmonary hypertension.[69]

If elective splenectomy is planned for a child or an adult, initiate immunization with *Haemophilus influenzae* type b vaccine at least 14 days before surgery.[70]

Immunize adults and children older than 2 years with polyvalent *Streptococcus pneumoniae* vaccine and quadrivalent meningococcal polysaccharide vaccine.

Evaluate patients who have a relapse after having an initially satisfactory response to splenectomy for the possible presence of an accessory spleen.[71, 72]

- An accessory spleen is strongly suggested if Howell-Jolly bodies appeared on the peripheral smear after splenectomy but are no longer present. However, the continued presence of Howell-Jolly bodies does not exclude an accessory spleen.
- Imaging techniques using radionucleotide-labeled sulfur colloid, heat-damaged RBCs, or, preferably, autologous platelets provide more useful information than standard imaging with CT scanning or MRI.

Consultations

Selecting a treatment program for immune thrombocytopenic purpura (ITP) requires knowledge of current options and consultation with a hematologist.

If 6 months of medical management fails to increase the platelet count to a safe range (about 30,000/µL), splenectomy becomes an option. Early consultation with a surgeon is useful for planning management.[73, 74]

If the platelet count is less than $10 \times 10^9/\text{L} (< 10 \times 10^3/\mu\text{L})$ or if the patient has other evidence of a clinically significant risk of serious hemorrhage, consult a radiologist to determine what noninterventional imaging procedures are available in case of emergency.

Medication Summary

The treatment of acute immune thrombocytopenic purpura (ITP) requires considerable individualization.[75] General approaches for children with acute ITP and adults with chronic ITP are discussed below.

**Recommended general approach for children with acute immune thrombocytopenic purpura**

For initial (induction) treatment, in patients with a platelet count of $20-30 \times 10^9/\text{L}$ [$20-30 \times 10^3/\mu\text{L}$] and/or mucocutaneous bleeding), one regimen is prednisone 4-8 mg/kg/d with the intent of a rapid and complete taper after 7-10 days or when the platelet count reaches $50 \times 10^9/\text{L}$ ($50 \times 10^3/\mu\text{L}$).
$10^3/\mu$L), whichever occurs first. In critical situations, an IV infusion of a corticosteroid may be preferable.

Second-line (maintenance) treatment is IV Rh immune globulin (IG), 75/µg/kg (off-label dose) for the Rh-positive patient or IVIG 1.0 g/kg for the Rh-negative patient. If the patient has clinically significant purpura or bleeding at presentation, consider infusing the first dose of IV RhIG or IVIG at the time of initial therapy with corticosteroids.

Repeat the infusions at 3- to 4-week intervals (maintenance) until a satisfactory platelet count is achieved. If the platelet count is not maintained after 3-4 infusions, the case might be refractory, and a different treatment should be considered. Conditions refractory to IV RhIG may respond to IVIG, and vice versa. If the patient's hemoglobin level decreases to 8.0 g/dL during treatment with IV RhIG, temporarily switch to IVIG until the level recovers. In this situation, the patient's condition should not be considered refractory to IV RhIG.

Conventional third-line treatment is splenectomy. However, recognizing the life-long potential adverse effects of splenectomy and the promising reports of responses to rituximab,[76, 77] the authors consider a course of rituximab 375 mg/m² per week for four doses (off-label indication) before splenectomy (which becomes fourth-line therapy).[78] Rituximab at a standard dose of 375 mg/m² per week for 4 weeks appears to be safe and effective, allowing nearly 40% of patients with ITP to achieve a long-term response and splenectomy-sparing effect in one study.[79]

**Recommended general approach for adults with chronic immune thrombocytopenic purpura**

Adults whose disease is not controlled with a prednisone-induced increase in platelet count that is maintained by IV RhIG or IVIG and whose conditions do not respond to four weekly infusions of rituximab are candidates for splenectomy. After these serial experiences, such patients are likely to have had thrombocytopenia for at least 6 months and, therefore, are categorized as having chronic ITP. Eltrombopag or romiplostim offer potential maintenance of safe levels of platelet counts for adults who qualify by having ITP for at least 6 months and whose conditions are refractory to conventional medical management (prednisone, IV RhIG, IVIG, rituximab), and whose platelet count is not maintained in a satisfactory range after splenectomy.[80]

The treatment of chronic, refractory ITP may introduce risks of toxicity from medications that are comparable in severity to the risks of untreated thrombocytopenia. These treatments also may impact adversely on the patient's quality of life.[81]

For patients with chronic refractory ITP who have access to investigational programs, the authors encourage them to participate in controlled clinical trials to support the development of effective treatments for this category.

**Thrombopoietin-receptor agonists**

Most conventional treatments for ITP act by decreasing destruction of autoantibody-coated circulating platelets. In contrast, thrombopoietin mimetics increase platelet counts in persons
with ITP by increasing the number of platelets produced and released by the bone marrow. Agents in this class include the thrombopoietin peptide mimetic romiplostim (Nplate) and the nonpeptide mimetic eltrombopag (Promacta). \[82, 83\]

Romiplostim was approved by the US Food and Drug Administration (FDA) in August 2008. It is a thrombopoiesis-stimulating protein Fc-peptide fusion protein ("peptibody") that increases platelet counts in patients with acute and chronic ITP without reports of significant toxicity. \[84, 33, 85\]

Eltrombopag is indicated for treatment of thrombocytopenia in patients with chronic ITP who have shown insufficient response to corticosteroids, immunoglobulins, or splenectomy. This drug was also approved by the FDA in 2008. \[86, 87\] In August 2015, the FDA expanded the indication for eltrombopag to include treatment of chronic ITP in patients 1 year of age and older who have not achieved an appropriate response with other medical therapy or splenectomy. \[56\]

**Corticosteroids**

**Class Summary**

Corticosteroids are the treatment of choice for initial management of acute ITP. These agents increase the platelet count by decreasing splenic uptake of autoantibody-coated platelets and by decreasing synthesis of autoantibody. Dosages must be tapered after a safe platelet count is achieved, and the drug is replaced with IV RhIG or IVIG to avoid serious complications of long-term steroid use.

*View full drug information*

**Prednisone (Deltasone, Orasone, Sterapred)**

Oral corticosteroid that is used most frequently because of its relatively low cost, known adverse effects, and long-term clinical record. DOC for initial treatment of ITP in children and adults. For aggressive treatment, may be combined with IV RhIG or IVIG. In emergency, replace PO prednisone with IV methylprednisolone.

*View full drug information*

**Methylprednisolone (Solu-Medrol)**

DOC for the initial management of severe bleeding tendency in ITP. IV is recommended when the most rapid and reliable treatment of ITP is required. In this situation, combine with IV RhIG in qualified Rh(D)-positive patients or IVIG in Rh(D)-negative patients or unqualified Rh(D)-positive patients.
**Blood Products**

**Class Summary**

Blood products are used to improve clinical and immunologic aspects of ITP. These products may decrease autoantibody production and increase solubilization and removal of immune complexes.

[View full drug information](#)

**IV RhIG (WinRho SDF)**

Specialized immunoglobulin product manufactured from pools of plasma from Rh(D)-negative persons and alloimmunized to D blood group antigen. Subjected to anion-exchange column chromatography to permit IV infusion and solvent-detergent treatment and nanofiltration to reduce infectivity by lipid-enveloped viruses. Induces immune RBC hemolysis in Rh(D)-positive recipients, decreasing function of mononuclear macrophages (reticuloendothelial blockade) and sparing immunoglobulin-coated platelets from splenic destruction.

[View full drug information](#)

**IVIG (Gamimune, Gammagard, Sandoglobulin)**

Large dose of 1 g/kg induces decreased function of mononuclear macrophages (reticuloendothelial blockade), sparing immunoglobulin-coated platelets from splenic destruction. Used with IV methylprednisolone to manage acute ITP in children. Decreased time to an increased platelet count compared with IV RhIG, but the difference does not appear to be clinically significant. Compared with IV RhIG, associated with more adverse effects, longer infusions, and increased cost, causing many hematologists to prefer IV RhIG as a supplement to corticosteroids, at least for Rh(D)-positive patients.

[View full drug information](#)

**Immunosuppressive Antimetabolites**

**Class Summary**

Immunosuppressive antimetabolites are used in patients with ITP to reduce production of abnormal autoantibodies.

[View full drug information](#)

**Azathioprine (Imuran)**

May be effective in some patients with ITP whose conditions do not or no longer have response to corticosteroids, IV RhIG, or IVIG. May be used with prednisone to reduce dose of prednisone or as another PO medication to delay splenectomy.
Synthetic Antineoplastic Drugs
Class Summary

Synthetic antineoplastic drugs are chemically related to nitrogen mustards. These agents inhibit cell growth and proliferation.

View full drug information

Cyclophosphamide (Cytoxan)

May be useful in some patients whose conditions do not or no longer have a response to corticosteroids, IV RhIG, IVIG, or splenectomy. Induces less of a decrease in platelet count than other immunosuppressive alkylating agents.

Androgens
Class Summary

The steroidogenic properties of androgens may modulate the immune system.

View full drug information

Danazol (Danocrine)

May impair the clearance of immunoglobulin-coated platelets and decreases autoantibody production. Increased platelet counts in 40-50% of patients, particularly postmenopausal women.

Monoclonal Antibodies
Class Summary

Monoclonal antibodies are chimeric murine-human monoclonal antibodies directed against CD20 on B lymphocytes.

View full drug information

Rituximab (Rituxan)

Chimeric monoclonal antibody directed against the CD20 antigen on the surface of normal and malignant B lymphocytes. Antibody is IgG kappa immunoglobulin with murine light- and heavy-chain variable sequences and human constant region sequences.

Thrombopoietin-Receptor Agonists
Class Summary

These new agents directly stimulate production of platelets by the bone marrow.[33]
Romiplostim (Nplate)

An Fc-peptide fusion protein (peptibody) that increases platelet production through binding and activation of the thrombopoietin (TPO) receptor, a mechanism similar to endogenous TPO. Indicated for chronic immune (idiopathic) thrombocytopenic purpura in patients who have had an insufficient response to corticosteroids, immunoglobulins, or splenectomy.

Eltrombopag (Promacta)

Oral thrombopoietin (TPO) receptor agonist. Interacts with transmembrane domain of human TPO receptor and induces megakaryocyte proliferation and differentiation from bone marrow progenitor cells. Indicated for thrombocytopenia associated with chronic idiopathic thrombocytopenic purpura in patients experiencing inadequate response to corticosteroids, immunoglobulins, or splenectomy. Not for use to normalize platelet counts, but used when clinical condition increases bleeding risk.

Complications

Inform patients with immune thrombocytopenic purpura (ITP) who have undergone splenectomy that their natural defense against acute bacterial infection is decreased.

Any fever, particularly when accompanied by signs or symptoms that suggest an illness more serious than the common cold, requires prompt medical attention and, possibly, early antibiotic treatment. Children with a fever (temperature of 38.8 °C [102 °F] or higher) should receive IV antibiotics until bacterial infection is excluded.

References


