Primary Immune Thrombocytopenia

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1. Diagnosis

Consider the diagnosis of primary immune thrombocytopenia in patients with isolated thrombocytopenia without a known precipitating cause.

1.1 Use patient history to make the diagnosis largely by excluding other causes.

Recommendations

- Use the history to explore other immune or nonimmune causes of thrombocytopenia, including:
  - Medication use (such as heparin, quinidine/quinine, and sulfonamides), including over-the-counter vitamin preparations or health supplements
  - Alcohol use
  - Viral illness (such as varicella, infectious mononucleosis, hepatitis C, and HIV), especially in children
  - Hepatitis may cause secondary ITP and other liver diseases (cirrhosis and portal hypertension are associated with nonimmune thrombocytopenia)
  - HIV risk factors, including injection drug use, sexual contact, transfusions
  - *H. pylori* infection, especially for mild to moderate thrombocytopenia
  - Exclude illnesses that can cause thrombocytopenia or are associated with secondary ITP (such as systemic lupus erythematosus)
  - Exposure to toxins such as benzene and its derivatives, nitrogen mustard, insecticides, organic hair dyes, and ionizing radiation
  - Acquired hematologic disorders, such as myelodysplastic syndrome, acute leukemia, chronic lymphocytic leukemia, or lymphoproliferative disorders
  - Inherited hematologic disorders, such as thrombocytopenia with absent radius, Bernard-Soulier syndrome, Gray platelet syndrome, Wiskott-Aldrich syndrome, May-Hegglin anomaly and other autosomal dominant thrombocytopenic disorders, Fanconi syndrome, and X-linked thrombocytopenia
  - Pregnancy is associated with the onset of ITP, or more commonly, gestational (physiologic) thrombocytopenia when mild, transient, and occurring towards the end of pregnancy
  - Transfusions within the last 5 to 14 days to exclude post-transfusion purpura
  - Ask about systemic symptoms such as weight loss, fevers, headache, arthralgias, and rash, as well as symptoms of hyper- or hypothyroidism, all of which can be associated with other related systemic or autoimmune diseases.
  - Use the history to explore the severity of bleeding symptoms, including:
    - The anatomic sites of bleeding, especially skin, mucous membranes, gastrointestinal, and vaginal
    - Bleeding following surgical challenges

Evidence

- The American Society of Hematology revised practice guidelines for ITP in 2011. This guideline is based on review of scientific evidence (where available) which was assessed using GRADE criteria (1).
- A study to determine the strength of clinical evidence for individual drugs as a cause of thrombocytopenia showed 515 patient case reports on patients with drug-induced thrombocytopenia (excluding heparin). In 247 case reports (48%), the drug appeared to be the cause. The reports included 98 drugs, most frequently quinidine, trimethoprim-sulfamethoxazole, and gold. However, many of the reports did not provide sufficient evidence to confirm drug-related thrombocytopenia (2).
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- Databases of published case reports of drug-induced thrombocytopenia ranking drugs according to the strength of clinical evidence for a causal relation to thrombocytopenia are available at this website or in a published compilation (2).
- A retrospective study based on clinical symptoms and laboratory parameters, which included platelet kinetics and mean platelet volume, describes an autosomal dominant macrothrombocytopenic disorder in which patients tend not to bleed and platelet counts do not respond to immune-modulating therapy (3).
- A narrative review describes a classification for hereditary thrombocytopenic disorders (4).
- A consensus statement addresses the investigation and management of adults and children with ITP (5).

**Rationale**
- Primary ITP is a diagnosis of exclusion. Thrombocytopenia may be immune (drug-induced, infection-associated) or nonimmune (congenital, alcohol- or toxin-induced, myelodysplasia). The presence of infection or other concomitant illnesses may also point to a cause.

**Comments**
- Immune thrombocytopenia was previously known as idiopathic or immune thrombocytopenic purpura.

**1.2 Use physical examination to help exclude other causes.**

**Recommendations**
- On physical exam look for:
  - Splenomegaly suggesting sequestration of platelets rather than ITP
  - Lymphadenopathy suggesting possible infection, lymphoproliferative disease, or cancer
  - Hepatomegaly that may indicate liver disease
  - Synovitis or arthritis suggesting an underlying rheumatologic disease
  - Fevers and/or neurologic changes suggesting TTP
  - Skeletal malformations suggesting a rare congenital thrombocytopenia

**Evidence**
- The presence of splenomegaly makes the diagnosis of ITP unlikely (6).
- The American Society of Hematology revised practice guidelines for ITP in 2011. This guideline is based on review of scientific evidence (where available) which was assessed using GRADE criteria (1).
- Impaired mental status is associated with TTP, as detailed in a recent review (7).

**Rationale**
- Thrombocytopenia is associated with hepatitis, cirrhosis, and portal hypertension, due to splenomegaly, and splenic sequestration of platelets, which are more common than ITP.
- The presence of synovitis or arthritis may indicate secondary ITP in the context of systemic lupus erythematosus or another rheumatologic disorder.
- Fever and neurologic impairment are found in TTP, which is characterized by thrombocytopenia, microangiopathic hemolytic anemia, and renal failure.

**1.3 Specifically assess patients for signs of bleeding.**

**Recommendations**
- On physical examination, look for:
  - Ecchymoses and petechiae on the skin
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- Mucous membrane, petechiae, or purpura in the mouth
- Hemorrhagic bullae of the oral mucous membranes or tongue
- Blood in the nose
- Neurologic findings suggesting intracranial hemorrhage
- Retinal hemorrhages
- Recognize that patients may be diagnosed with ITP during a ‘routine’ medical examination.
- See figure Petechia due to Thrombocytopenia.

Evidence

- Based on accepted clinical practices and the 2011 consensus statement of the American Society of Hematology (1).
- A prospective study explored demographic and comorbid clinical factors in 205 patients with ITP. Of the 186 adults in the study, 87 (47%) had been diagnosed with ITP incidentally during a routine medical examination, while 96 (52%) presented with bleeding symptoms (8).
- Using a mathematical model applied to patients with ITP identified by a systematic literature search, age-adjusted rates of fatal hemorrhage were 0.004, 0.012, and 0.31 cases per patient-year for age groups younger than 40, 40 to 60, and older than 60, respectively (9).

Rationale

- Patients may be asymptomatic or have minimal symptoms at presentation.
- It is important to assess the level of bleeding to determine the severity of the disease and the intensity of treatment.

1.4 Recognize that there is no single diagnostic test for ITP but that CBC is essential in supporting the diagnosis.

Recommendations

- Obtain CBC and examine a peripheral blood film to confirm thrombocytopenia and determine that the leukocyte count and red cell morphology are normal.
- See table Laboratory Tests to Support the Diagnosis of Primary Immune Thrombocytopenia.

Evidence

- A prospective study examined the likelihood of developing ITP among 217 individuals with mild thrombocytopenia (platelet counts between $100 \times 10^9$ cells/L and $150 \times 10^9$ cells/L). The 10-year probability of developing a persistent platelet count $<100 \times 10^9$ cells/L was 6.9% (CI, 4.0% to 12.0%) (10).
- A consensus statement established the cutoff platelet count for ITP as $<100 \times 10^9$ cells/L (11).
- See the 2011 American Society of Hematology consensus statement (1).

Rationale

- Thrombocytopenia (platelet count $<100 \times 10^9$ cells/L) is an essential feature of ITP.
- The leukocyte count is normal in ITP. However, the presence of anemia does not exclude ITP if it can be explained by iron deficiency or bleeding, or if there is a known hemoglobinopathy such as sickle cell disease.
- Autoimmune hemolytic anemia may be present concomitantly with ITP, known as Evan’s syndrome.
- Fragmented red cells with thrombocytopenia suggest microangiopathic hemolytic anemia rather than ITP.
1.5 Examine the peripheral blood smear to confirm the diagnosis. C

**Recommendations**

- Examine the blood smear to:
  - Confirm thrombocytopenia and exclude clumping, which is indicative of a laboratory-only phenomenon called pseudothrombocytopenia
  - Confirm the presence of normal erythrocyte and leukocyte number and morphology; in particular, exclude:
    - Microangiopathic changes in erythrocytes
    - The presence of nucleated erythrocytes and early or abnormal myeloid forms
    - Leukocyte inclusion bodies
  - See table [Laboratory Tests to Support the Diagnosis of Idiopathic Thrombocytopenic Purpura](#).
  - See figure [Pseudothrombocytopenia](#).
  - See figure [Normal Platelets on Peripheral Blood Smear](#).
  - See figure [Giant Platelet on Peripheral Blood Smear](#).

**Evidence**

- Consensus (1; 5).

**Rationale**

- In ITP, the erythroid and myeloid morphology is normal.
- The presence of schistocytes is associated with microangiopathic hemolytic anemia, such as TTP and hemolytic uremic syndrome, rather than ITP.
- The presence of nucleated erythrocytes and early myeloid forms suggests a myelophthisic process as seen in neoplastic and metastatic disease, lymphoma, granulomatous disease, and infections of the bone marrow.
- The presence of pseudo-Pelger-Huet anomaly and hypogranulation of myeloid cells suggests myelodysplastic syndrome.
- Leukocyte inclusion bodies called Döhle bodies are suggestive of a hereditary thrombocytopenia syndrome (such as May-Hegglin anomaly).

1.6 Consider a bone marrow aspiration and biopsy in patients with atypical findings to identify an alternate diagnosis. Bone marrow aspiration and biopsy is not necessary to establish the diagnosis in patients presenting with typical ITP. C

**Recommendations**

- Consider a bone marrow aspiration and biopsy to identify an alternative diagnosis if atypical findings are present in history, physical exam, or lab studies, including abnormalities on the peripheral blood smear.
- See table [Laboratory Tests to Support the Diagnosis of Idiopathic Thrombocytopenic Purpura](#).

**Evidence**

- These recommendations are drawn from the 2011 American Society of Hematology guidelines (1).
- A bone marrow examination is not required to establish the diagnosis in patients with history, physical, lab, and peripheral smear findings consistent with ITP (1).
- Over a 1-year period in 2003, health care providers prospectively collected data on adverse events associated with bone marrow aspiration and biopsy procedures. Of 19,259 procedures, there were
16 adverse events, 1 of which occurred in a patient with ITP and a platelet count of $6 \times 10^9$ cells/L (12).

**Rationale**

- Bone marrow biopsy is not essential for the diagnosis but can help exclude underlying diagnoses if atypical features are present.
- Bleeding complications following bone marrow biopsy in patients with ITP are very rare and generally easily controlled.

**Comments**

- On bone marrow examination in patients with ITP, typical findings are normal or increased numbers of megakaryocytes, normal morphology and relative percentages of the myeloid and erythroid precursors, and absence of extrinsic nonhematopoietic cells.

1.7 **Consider testing for* H. pylori* infection in certain geographic locations.**

**Recommendations**

- In some patients with ITP who do not respond to initial therapy or who relapse, consider a $^{13}$C urea breath test to test for infection with *H. pylori*.

**Evidence**

- In a systematic review of 696 patients with ITP, 42.7% (CI, 31.8% to 53.9%) achieved a platelet count response following *H. pylori* eradication; the response rate was lower in patients with severe thrombocytopenia (defined in this review as $<30 \times 10^9$ cells/L) (13).

**Rationale**

- Diagnosis of *H. pylori* infection and its treatment may be an alternative therapy for ITP and may allow some patients to avoid immunosuppressive therapy.
- Proposed mechanisms of *H. pylori*-induced ITP are antibody cross-reactivity with platelet autoantigens, activation of autoreactive B-cells, and enhancement of monocyte phagocytic activity.

**Comments**

- There seems to be geographic variability in the prevalence of *H. pylori* and in the serotype of the *H. pylori* bacteria, such that in certain countries, including Japan, rates of platelet count responses following *H. pylori* eradication in patients with ITP have been significant. In other countries, response rates are much lower.

1.8 **Exclude other causes of thrombocytopenia.**

**Recommendations**

- History, physical, and lab studies should exclude other diseases or conditions associated with thrombocytopenia, such as medications or liver disease, which are more common than ITP.
- See information on patient history and physical exam.
- See table Differential Diagnosis of Primary Immune Thrombocytopenia.

**Evidence**

- Consensus (1; 5).

**Rationale**

- The diagnosis of primary ITP is made when other causes of thrombocytopenia have been excluded.
2. Consultation

Consult a hematologist or oncologist for patients with severe thrombocytopenia (<50 × 10^9 cells/L) when there is diagnostic uncertainty. Obtain consultation with an appropriate specialist if there is no response to initial therapy or other hematologic disorders develop.

2.1 Consider consultation by a hematologist or oncologist for severe thrombocytopenia or if there are abnormalities in the number or morphology of other cell lines.

Recommendations

- Consult a hematologist or oncologist if there is:
  - Thrombocytopenia with platelet counts <50 × 10^9 cells/L
  - Leukopenia
  - Leukocytosis
  - Anemia not due to blood loss or iron deficiency
  - Morphologic abnormalities of the erythroid or myeloid series
  - Presence of nucleated erythrocytes or myeloid precursors on the peripheral blood smear

Evidence

- Myelodysplastic syndrome can present with isolated thrombocytopenia (15).
- Retrospective studies have shown that platelet count correlates with clinical bleeding, that clinically significant bleeding occurs in less than 5% of patients with platelet counts of >10 × 10^9 cells/L, and rarely in patients with platelet counts <50 × 10^9 cells/L (16).
- In a cohort of 117 patients with chronic ITP, 49 with platelet counts <30 × 10^9 cells/L were seen without treatment, and none of these had hemorrhagic complications over a mean follow-up of 30 months (17).
- Guidelines suggest that treatment is indicated for patients with ITP and a platelet count <30 × 10^9 cells/L. Threshold platelet counts may be higher for patients with bleeding (1).

Rationale

- There is no established cutoff in platelet count that correlates precisely with bleeding risk.
- Consultation will aid in the diagnosis and management of hematologic malignancies or microangiopathic disorders associated with thrombocytopenia and with the treatment of severe ITP.

2.2 Obtain hematologic consultation if there is no response to initial therapy.

Recommendations

- Obtain hematologic consultation if there is no increase in platelet count after 1 to 2 weeks of prednisone or after initial dose of IVIG.

Evidence

- Consensus.

Rationale
• The patient may have refractory ITP or another hematologic disorder.

2.3 Obtain surgical consultation for splenectomy if medical therapy is ineffective.

Recommendations
• Note that splenectomy is recommended for patients with persistent platelet counts <10 × 10⁹ cells/L for 4 to 6 weeks and for patients who have had ITP for 3 months with persistent severe thrombocytopenia (platelet count <30 × 10⁹ cells/L) despite treatment.

Evidence
• Splenectomy has been shown to be effective in leading to the resolution of ITP in observational studies (6; 21; 45; 56; 60; 61; 62; 63; 64); however, there are not enough data to make evidence-based recommendations on the timing of splenectomy in ITP.
• Recommendations are based on the American Society of Hematology Consensus statement (1) and the international consensus statement (5).
• A systematic review of 135 case series of splenectomy showed that complete remission was reported in 66% (1731 of 2623) of patients. Younger age was an independent predictor of a platelet count response in a multivariate analysis. Other preoperative characteristics, including response to corticosteroids, were not predictive of response to splenectomy (46).
• A retrospective cohort study of 30 consecutive patients with ITP reported that a good or excellent response to IVIG, defined as the achievement of a platelet count >50 × 10⁹ cells/L or >150 × 10⁹ cells/L, respectively, predicted a good or excellent response to splenectomy at 1 year (65).

Rationale
• Splenectomy results in a sustained platelet count response in approximately 60% of patients.

Comments
• Laparoscopic splenectomy is a valid alternative to conventional splenectomy in the treatment of ITP (48).
• With the development and introduction of new drugs for ITP, such as anti-CD20 monoclonal antibody and thrombopoietin mimetics, splenectomy may be delayed or avoided (50).
3. Hospitalization

Hospitalize patients with severe bleeding or severe thrombocytopenia with mucous membrane bleeding.

3.1 Hospitalize patients with severe life-threatening bleeding, regardless of platelet count.

Recommendations

- Hospitalize patients with mucous membrane bleeding and new-onset severe thrombocytopenia (typically, platelet counts <20 × 10⁹ cells/L).
- Hospitalize patients with bleeding (e.g., vaginal, epistaxis) requiring clinical intervention, even if platelet count is >20 × 10⁹ cells/L.
- Begin therapy (see section on Therapy) to halt bleeding and prevent complications of bleeding.
- Note that hospitalization is not required for patients with platelet counts >20 × 10⁹ cells/L who are asymptomatic or have only minor bleeding, such as epistaxis that resolves in less than 15 minutes, gingival bleeding with toothbrushing, or petechiae or ecchymoses on the skin.

Evidence

- There is no direct evidence that hospitalization is associated with improved survival or outcome in patients with ITP. Recommendations are based on consensus (1).

Rationale

- Severe bleeding complications are less likely in patients with platelet counts >20 × 10⁹ cells/L who are asymptomatic or have only minor bleeding.
4. Therapy

Consider careful observation for some patients, advise patients on the avoidance of activities associated with a high risk for bleeding, consider drug therapy to improve the platelet count and decrease the risk for bleeding, and consider splenectomy for patients in whom steroid therapy is unsuccessful.

4.1 Consider careful observation for patients at low risk for bleeding.

Recommendations

- Recognize that mild ITP is often associated with a good prognosis.
- For patients with platelet counts >50 × 10⁹ cells/L who have no history of bleeding, consider careful observation with regular visits and platelet count determinations.

Evidence

- In a cohort study of 152 patients previously treated with a defined algorithm for ITP and followed for a median of 10.5 years, only those patients with refractory disease (n=12) had excess mortality risk compared with the general population (RR, 4.2 [CI, 1.7 to 10.0]). Patients with refractory or persistent ITP (n=20) had excess hospitalizations (18).

Rationale

- Treatment of ITP is associated with side effects that can be safely avoided for many patients with mild ITP.

4.2 Counsel patients to abstain from alcohol and avoid certain medications, contact sports, and other activities that increase risk for bleeding.

Recommendations

- Advise patients to:
  - Abstain from drinking alcohol
  - Avoid contact sports and other recreational activities associated with increased risk for trauma
  - Avoid aspirin, NSAIDs, and anticoagulants unless otherwise advised by a physician
  - In some patients, increase the target platelet count for treatment when necessary to accommodate lifestyle activities and the need for anticoagulation or antiplatelet agents.

Evidence

- Consensus.

Rationale

- Alcohol may impair platelet function and cause or exacerbate thrombocytopenia; heavy alcohol use also can lead to accidents and traumatic hemorrhage.
- Avoiding certain sports decreases risk for traumatic hemorrhage.
- Aspirin, NSAIDs, and anticoagulants increase risk for bleeding.

4.3 Recognize that corticosteroids are the initial therapy of choice.

Recommendations

- Begin initial therapy with prednisone, 1 to 2 mg/kg·d, in adults with platelet counts <20 to 30 × 10⁹ cells/L and/or purpura or other bleeding.
• If there is a response with a normalization of the platelet count over 1 to 2 weeks, taper by 5 to 10 mg/week.
• Consider high-dose dexamethasone, 40 mg/d for 4 days, as a reasonable alternative to prednisone.
• See table Drug Treatment for Primary Immune Thrombocytopenia.

Evidence
• There are no randomized trials showing a benefit of corticosteroids on overall morbidity or mortality.
  • A randomized trial of prednisone 0.5 mg/kg·d vs. 1.5 mg/kg·d showed no significant difference in platelet counts between the low- or high-dose arms in adults (30% vs. 34% complete response, respectively) (19).
  • A randomized trial of low (0.25 mg/kg·d) vs. high (1 mg/kg·d) prednisone for 3 weeks, with taper and discontinuation by the end of 4 weeks, showed a complete response (platelet count >100 × 10⁹ cells/L for at least 6 months) in 74% of adults, with no difference between the low- and high-dose groups (20).
  • In retrospective studies in adults, corticosteroids have been associated with a complete response rate of 30% to 38%, an overall response rate (platelet counts >50 × 10⁹ cells/L) of 65% to 80%, and prolonged remission rates of 15% to 20% (21; 22; 23; 24; 25).
  • Corticosteroids have been recommended in the 2011 American Society of Hematology guidelines (1).
  • A randomized study of IVIG (0.7 g/kg·d for 3 days) vs. high-dose methylprednisolone (15 mg/kg·d for 3 days) followed by a second randomization to prednisone (1 mg/kg·d) vs. placebo showed that response to IVIG was more rapid: more patients achieved a platelet count >50 × 10⁹ cells/L within the first 5 days, and the number of days with a platelet count >20 × 10⁹ cells/L between days 1 and 21 was higher in the group receiving IVIG. Patients receiving subsequent prednisone therapy were more likely to have a platelet count >50 × 10⁹ cells/L on day 21 than patients treated with placebo. There was no difference in long-term outcome (26).
  • The results of two noncontrolled, prospective cohort studies (one single center [n=37] and one multicenter [n=95]) examining repeated cycles of high-dose dexamethasone were published as a single report. In the single-center study, previously untreated patients with newly diagnosed ITP were given dexamethasone, 40 mg/d iv for 4 consecutive days, repeated every 28 days for six cycles. Of the 37 patients, 23 (62.2%) achieved a complete response, defined as a platelet count >150 × 10⁹ cells/L, and, of those, 20 had a prolonged complete response lasting for a median of 26 months. In the multicenter study, previously untreated patients with ITP were given oral or intravenous dexamethasone as a single daily dose of 40 mg for 4 consecutive days every 14 days for four courses. Of the 95 patients, 58 (64.5%) achieved a complete response, and, of those, 53 had a prolonged response lasting for a median of 8 months. In both studies, patients were supplemented with additional corticosteroids if needed (27).

Rationale
• Proposed mechanism is inhibition of autoimmune destruction of platelets.

Comments
• The prolonged use of corticosteroids is associated with significant side effects, including osteoporosis, hypertension, diabetes, and glaucoma.

4.4 Consider using intravenous immune globulin in selected patients.

Recommendations
• Use IVIG, 1 to 2 g/kg (administered in divided doses given over 2 to 5 days), in patients who are refractory to treatment with corticosteroids, before surgical procedures, or as initial treatment for patients with severe bleeding.

• See table Drug Treatment for Primary Immune Thrombocytopenia.

**Evidence**

• Most IVIG studies have been done in children (28; 29).

• Studies in adults show that most patients achieve increases in platelet counts (30; 31; 32).

• A randomized study showed that treatment with IVIG at 1g/kg or 2g/kg yielded similar platelet count responses (33).

• A randomized study of IVIG (0.7 g/kg·d for 3 days) vs. high-dose methylprednisolone (15 mg/kg·d for 3 days) followed by a second randomization to prednisone (1 mg/kg·d) vs. placebo showed that response to IVIG was more rapid: more patients achieved a platelet count >50 × 10^9 cells/L within the first 5 days, and the number of days with a platelet count >20 × 10^9 cells/L between days 1 and 21 was higher in the group receiving IVIG. Patients receiving subsequent prednisone therapy were more likely to have a platelet count >50 × 10^9 cells/L on day 21 than patients treated with placebo. There was no difference in long-term outcome (26).

• A systematic review and meta-analysis of randomized, controlled trials comparing the efficacy of corticosteroids with the efficacy of IVIG for the initial treatment of children with acute ITP (n=401) reported that the achievement of a platelet count >20 × 10^9 cells/L at 48 hours was 26% less likely among children treated with corticosteroids compared with children treated with IVIG (34).

**Rationale**

• IVIG rapidly increases the platelet count in most patients.

**4.5 Consider RhIG for patients with blood group Rh(+) who have not had a splenectomy.**

**Recommendations**

• Consider RhIG, 50 to 75 µg/kg, for some patients with ITP:
  • Patients who are Rh(+) and have not had a splenectomy
  • Patients in whom splenectomy is not feasible
  • Patients for whom corticosteroids have failed or other options are unavailable, in lieu of IVIG

• Be aware that complications related to hemolysis are a concern with RhIG.

• See table Drug Treatment for Primary Immune Thrombocytopenia.

**Evidence**

• A randomized clinical trial compared routine care (prednisone) with RhIG in 70 newly diagnosed patients with ITP with platelet counts <30 × 10^9 cells/L. Rates of splenectomy were similar (38% vs. 42%), but time to splenectomy was 36 days in the routine care group and 112 days in patients who had been treated with RhIG (35).

• A randomized trial of 105 children who had newly diagnosed ITP and were Rh(+) found that RhIG, 75 µg/kg, was as effective as IVIG, 0.8 g/kg, and more effective than RhIG, 50 µg/kg, at achieving a platelet count >20 × 10^9 by 24 hours (36).

**Rationale**

• RhIG therapy leads to sustained increases in platelet counts in some patients who have not had a splenectomy.

• RhIG may allow for deferral of splenectomy.
• RhIG can be administered much faster (10 to 15 minutes) than IVIG (approximately 4 hours).

Comments
• Hemolysis and varying degrees of anemia are expected side effects of RhIG. Rare cases of disseminated intravascular coagulation and death have been reported (37). This has led to a boxed warning for this drug and removal from several European markets.

4.6 Administer appropriate vaccinations before splenectomy.

Recommendations
• Vaccinate patients against S. pneumoniae, N. meningitidis, and H. influenzae type b at least 2 weeks prior to splenectomy.
• Note that revaccination with pneumococcal vaccine should be done every 5 years.
• See table Drug Treatment for Primary Immune Thrombocytopenia.

Evidence
• Case series of patients undergoing splenectomy for hereditary spherocytosis showed 1 death per 5000 patient-years (38).
• A literature review showed a 1.8% risk for fulminant sepsis and retrospective study showed 1.5% or 0.17 cases of sepsis per 100 patient-years (39).
• There are no randomized trials studying the need for revaccination; however, case series have shown that antibody levels to specific pneumococcal and H. influenzae antigens decline over time. In one series of 149 vaccinated splenectomized patients, 50% had anti-pneumococcal and 60% had anti-H. influenzae antibody levels in the range thought to be protective from infection (40, 41).
• The Center for Disease Control and Prevention's Advisory Committee on Immunization Practices provides recommendations for the use of vaccines and immune globulins for immunocompromised persons (42).
• Asplenic patients are at increased risk for infection. In a pooled analysis of 19,680 splenectomized patients from 78 studies, the incidence of post-splenectomy septicemia and/or meningitis was 3.2% after a median follow-up of 6.9 years (43).
• In a population cohort study of 3812 splenectomized patients, the adjusted odds ratio for the risk for any infection requiring hospitalization among those with ITP compared with non-splenectomized ITP patients was 2.6 (CI, 1.3 to 5.1) in the first 90 days; the hazard ratio was 1.0 (CI, 0.5 to 2.0) from 91 days to 1 year and 1.4 (CI, 1.0 to 2.0) beyond 1 year (44).

Rationale
• Splenectomy is associated with a risk for infection with bacterial organisms.

4.7 Consider splenectomy for patients who do not respond to, or who relapse following, first-line corticosteroid-based treatments.

Recommendations
• Note that splenectomy is recommended for patients with ITP in whom corticosteroid-based therapy has failed. Splenectomy is often considered for patients who have had ITP for 12 months or more, after which time spontaneous remissions are unlikely.
• Vaccinate patients undergoing splenectomy against S. pneumoniae, N. meningitidis, and H. influenzae type b at least 2 weeks prior to surgery (see previous section regarding vaccination before splenectomy).

Evidence
• Splenectomy has been shown to be effective in up to 80% of patients with a sustained response for up to 5 years achieved in 66% of patients (45; 46; 47).

• Recommendations are based on the American Society of Hematology 2011 Guidelines (1). A consensus statement on terminology of ITP defined chronic ITP as lasting longer than 12 months (11).

• A systematic review of 135 case series of splenectomy showed that complete remission was reported in 66% (1731 of 2623) of patients. Younger age was an independent predictor of a platelet count response in a multivariate analysis. Other preoperative characteristics, including response to corticosteroids or IVIG, were not predictive of response to splenectomy (46).

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• In a population cohort study of 3812 splenectomized patients, the adjusted odds ratio for the risk for any infection requiring hospitalization among those with ITP compared with non-splenectomized ITP patients was 2.6 (CI, 1.3 to 5.1) in the first 90 days; the hazard ratio was 1.0 (CI, 0.5 to 2.0) from 91 days to 1 year and 1.4 (CI, 1.0 to 2.0) beyond 1 year (44).

Rationale
• Splenectomy results in a sustained platelet count response in approximately 66% of patients.

Comments
• Laparoscopic splenectomy is a valid alternative to conventional splenectomy in the treatment of ITP (48) and is associated with less postoperative pain, shorter hospital stays, and decreased wound complication rates (49).

• With the development and introduction of new drugs for ITP, such as anti-CD20 monoclonal antibody (rituximab) and thrombopoietin mimetics, splenectomy may be delayed or avoided (1; 50).

• Immediate perioperative complications following splenectomy include pneumonia, subphrenic abscess, or pleural effusion (4% of patients); major bleeding (1.5%); and thromboembolism (1%). Perioperative mortality is approximately 1% with laparotomy and 0.2% with laparoscopic splenectomy (46).

4.8 Recognize that patients with refractory ITP for whom corticosteroids and splenectomy are unsuccessful or in whom splenectomy is contraindicated may require therapy with other agents.

Recommendations
• Recognize that there is no single established algorithm for treating refractory ITP and that drug treatment should be based on individual needs and the side effect profiles of the medications.

• Consider treatment with thrombopoietin receptor agonists, such as romiplostim and eltrombopag, administered as maintenance therapy.

• Consider treatment with rituximab, 375 mg/m² once weekly, for 4 weeks.

• Treat patients who relapse after splenectomy with prednisone at the lowest doses possible to maintain a safe platelet count.

• Understand that some patients will not respond to corticosteroids or will need doses higher than 10 to 15 mg/d, which may lead to unacceptable side effects and necessitate treatment with other agents.
• Recognize that some patients who do not respond to other drug therapy continue to respond to high dose IVIG, although responses are generally transient, lasting a few weeks, and therapy is expensive.

• Give platelet transfusion to patients who are severely thrombocytopenic and experiencing serious or life-threatening bleeding.

• Consider these other options for drug treatment of patients with ITP that is refractory to corticosteroids and splenectomy:
  - Danazol, 200 mg qid
  - Immunosuppressive agents, such as azathioprine, 150 mg/d; mycophenolate mofetil, 1.5 to 2 g/d; or cyclosporine, 2 to 3 mg/kg·d
  - Cytoreductive agents, such as vincristine, 1 to 2 mg/week, iv; vinblastine, 5 to 10 mg/week; oral cyclophosphamide, 2 mg/kg·d; or high-dose intravenous cyclophosphamide, 1 to 1.5 mg/m² every 4 weeks

• See table Drug Treatment for Primary Immune Thrombocytopenia.

Evidence

• The 2011 American Society of Hematology guidelines provide recommendations for the treatment of patients who require additional treatment following splenectomy (1).

• Two randomized trials showed that in splenectomized and non-splenectomized patients with ITP and a platelet count <30 × 10⁹ cells/L, 16 of 42 splenectomized patients and 24 of 41 non-splenectomized patients given romiplostim achieved a durable platelet count response (platelet count ≥50 × 10⁹ cells/L during 6 of the last 8 weeks of treatment) compared with 0 of 21 splenectomized patients and 1 of 21 non-splenectomized patients given placebo (51).

• In a randomized trial of romiplostim (n=157) or standard of care (n=77) for non-splenectomized adults with ITP, patients receiving romiplostim had a significantly lower incidence of treatment failure (18 of 157 patients [11%]) than those receiving the standard of care (23 of 77 patients [30%]; P<0.001) (OR with romiplostim, 0.31 [95% CI, 0.15 to 0.61]). Fewer splenectomies were performed in the romiplostim group, which had a lower rate of bleeding events, fewer blood transfusions, and greater improvements in the quality of life (52).

• A randomized, placebo-controlled trial of eltrombopag (n=197) in patients with ITP for at least 6 months’ duration and a platelet count <30 ×10⁹ cells/L showed that 106 (79%) patients in the eltrombopag group responded to treatment at least once during the study, compared with 17 (28%) patients in the placebo group. The odds of responding were greater in patients in the eltrombopag group compared with those in the placebo group throughout the 6-month treatment period (OR, 8.2 [99% CI, 3.59 to 18.73]; P<0.0001) (53).

• Concerns have been raised over the increased bone reticulin found in 10 of over 271 patients included in the romiplostim trials and in 7 of 117 patients in the eltrombopag trials. Liver function test abnormalities were seen in 13% of patients treated with eltrombopag (5).

• A 2004 systematic review of the literature, including 90 articles with 656 patients treated with 22 therapies, showed that evidence supporting effectiveness and safety of any treatment in patients with chronic ITP is minimal (54).

• A 2007 systematic review of studies examining the effect of rituximab in ITP concluded that rituximab was associated with the achievement of an overall response (platelet count >50 × 10⁹ cells/L) in 62.5% of patients and a complete response (platelet count >150 × 10⁹ cells/L) in 43.6% of patients (55). This review was limited by the lack of controlled studies.

• In a retrospective analysis, the rate of fatal hemorrhage patients with a platelet count <30 × 10⁹ cells/L was 0.019 cases per patient-year. Patients who did not respond to therapy at 2 years had a 4-fold increase in mortality compared to the general population (56).
In a study of 105 patients with refractory ITP after splenectomy (platelets <30 × 10^9 cells/L), 75% eventually achieved remission. In 51 (49%) patients, remission continued after therapy was stopped, and in 24 (23%) patients, continued therapy with low-dose corticosteroids or danazol was needed to maintain remission (57).

Rationale

- Pharmacologic agents may be necessary to increase platelet counts to a level that is safe in individual patients with chronic ITP for whom corticosteroids and splenectomy have failed.
- Patients with platelet counts <20 × 10^9 cells/L are at an increased risk for hemorrhage.
- Treatment modalities are targeted to various mechanisms of disease, and are aimed at reducing autoantibodies to platelets, preventing destruction of platelets by macrophages, removing autoreactive B-cells, improving T-cell abnormalities, and increasing platelet production.

4.9 Recognize that eradication of *H. pylori* has been shown to induce platelet recovery in some patients with ITP.

Recommendations

- Consider testing for *H. pylori* infection in regions where infection is endemic, and, if results are positive, treating with one of triple drug regimens shown to be effective.
- See table Drug Treatment for Primary Immune Thrombocytopenia.

Evidence

- In a 2009 systematic review of 696 patients with ITP, 42.7% (CI, 31.8% to 53.9%) achieved a platelet count response following *H. pylori* eradication; the response rate was lower in patients with severe thrombocytopenia (defined in this review as <30 × 10^9 cells/L) (13).
- In a 2007 systematic review of 788 patients with ITP from 17 studies (16 prospective cohorts and 1 randomized trial), *H. pylori* eradication was associated with an increase in platelet count of 41 × 10^9 cells/L (CI, 21 to 61 × 10^9 cells/L) compared with untreated patients, 52 × 10^9 cells/L (CI, 34 to 70 × 10^9 cells/L) compared with patients who failed to respond to eradication, and 46 × 10^9 cells/L (CI, 28 to 65 × 10^9 cells/L) compared with *H. pylori*-negative patients (58).

Rationale

- Eradication of *H. pylori* may decrease antigenic stimulus for autoantibody formation and autoimmune destruction of platelets.

Comments

- These recommendations are based only on small case series.
- There seems to be geographic variability in the prevalence of *H. pylori* and in the serotype of the *H. pylori* bacteria, such that in certain countries, including Japan, rates of platelet count responses following *H. pylori* eradication in patients with ITP have been significant. In other countries, response rates are much lower.
5. Patient Counseling

Educate patients about the mechanism, complications, and treatment of their disease.

5.1 Teach patients to recognize symptoms of bleeding that may indicate a decreased platelet count.

Recommendations
- Teach patients how to recognize petechiae, oral mucosal purpura (oral blood blisters), ecchymoses, epistaxis, gingival bleeding, rectal bleeding, and excess vaginal bleeding.

Evidence
- Consensus.

Rationale
- Patients who recognize that hemorrhagic symptoms may indicate decreasing platelet counts will seek medical attention.

5.2 Teach patients to recognize the immunosuppressive effects of therapy.

Recommendations
- Teach patients to recognize that steroid use leads to immunosuppressive effects, with increased susceptibility to infections and poor wound healing.
- Inform splenectomized patients that they are more susceptible to infection, especially with encapsulated organisms such as pneumococcus.
- Consider suggesting that splenectomized patients wear a medical information bracelet or the equivalent.
- Educate patients and their families to recognize the signs of serious infection:
  - Fever
  - Cough
  - Shortness of breath
  - Altered mental status
  - Headache
  - Stiff neck
  - Photophobia
- Urge patients to avoid contact with children or adults with meningitis, pneumococcal pneumonia, and other bacterial illnesses.

Evidence
- Consensus.
- Guidelines from experienced practitioners (59).

Rationale
- Patients on steroids or after splenectomy are immunocompromised.
6. Follow-up

Monitor all patients for recurrent thrombocytopenia after therapy.

6.1 Schedule, monitor, and taper medication appropriately for all patients initially started on corticosteroids.

Recommendations

- After an initial response to corticosteroids with normalization of platelets, and 1 to 2 weeks of therapy at 1 to 2 mg/kg·d of prednisone, taper prednisone by 5 to 10 mg/week for 4 weeks and 5 mg/week thereafter, provided the platelet count remains stable.
- Monitor for signs and symptoms of bleeding and check CBC weekly or biweekly during steroid taper.
- Recognize that the tapering schedule may need adjustment depending upon the individual clinical situation.

Evidence

- Consensus.

Rationale

- Careful tapering of steroids is necessary to decrease the possibility of relapse.

6.2 Monitor symptoms, signs and CBC in patients with disease remission or chronic ITP who do not require treatment.

Recommendations

- Monitor patients who have achieved normal platelet counts after therapy for signs or symptoms of bleeding.
- Ask about petechiae, purpura (including oral blood blisters), epistaxis, gingival bleeding, and menstruation.
- Look for ecchymoses, purpura, and petechiae.
- If patient has achieved a complete response after steroids or splenectomy, perform a follow-up CBC every month for 6 months, every 2 months for 6 months, every 3 months for 6 months, then every 6 months for 1 year.
- Patients with chronic ITP who do not require treatment may be followed every 3 months. Patients with bleeding or lower platelet counts (<50 x 10^9 cells/L) may need to be followed biweekly or monthly.

Evidence

- A prospective study of 245 patients with ITP was performed in a population-based cohort in England, with a median follow-up of 60 months. The study showed that 135 patients (55%) responded to first-line therapy, 30 (12%) underwent splenectomy, 4 (1.6%) died from bleeding complications, and 17 (7%) had minimal or no response to therapy. Platelet count at diagnosis did not predict outcome (66).
- Based on case series, 10% to 40% of patients will relapse after splenectomy, with half of these relapses occurring within the first 6 months (64).
- Platelet response of >150 x 10^9 cells/L on the third day after splenectomy (64) or >500 x 10^9 cells/L on the tenth day after splenectomy (67) correlate with long-term improvement in platelet counts.
• In a retrospective study, 75% of patients who were splenectomized had a partial or complete response at 2 years, and the long-term remission rate was 66% (56).

• In a study of 105 patients with refractory ITP after splenectomy (platelets <30 × 10⁹ cells/L), 75% eventually achieved remission. Median time to remission was 46 months. Seventeen (16%) of these patients died of bleeding complications associated with thrombocytopenia or therapy-related complications (57).

Rationale
• Despite achieving remission, some patients will relapse and present with signs and symptoms of bleeding.
References


Primary Immune Thrombocytopenia


Primary Immune Thrombocytopenia


Primary Immune Thrombocytopenia

Glossary

ANA
antinuclear antibody

bid
twice daily

CBC
complete blood count

CI
confidence interval

CT
computed tomography

DNA
deoxyribonucleic acid

EBV
Epstein-Barr virus

EDTA
ethylene diamine tetra-acetic acid

ESR
erythrocyte sedimentation rate

G-CSF
granulocyte colony-stimulating factor

HELLP
hemolysis, elevated liver enzymes, and low platelet (count)

HIV
human immunodeficiency virus

HUS
hemolytic-uremic syndrome

IgA
immunoglobulin A

IgE
immunoglobulin E

IgG
immunoglobulin G

ITP
immune thrombocytopenia, also called immune thrombocyticopenic purpura or idiopathic thrombocyticopenic purpura

iv
intravenous

IVIG
intravenous immunoglobulin

NSAID
nonsteroidal anti-inflammatory drug

PT
plasma thromboplastin

PTT
partial thromboplastin time
Primary Immune Thrombocytopenia

qd
once daily

qid
four times daily

RhIG
rhesus immune globulin

RR
relative risk

tid
three times daily

TSH
thyroid-stimulating hormone

TTP
thrombotic thrombocytopenic purpura
## Laboratory Tests to Support the Diagnosis of Primary Immune Thrombocytopenia

<table>
<thead>
<tr>
<th>Test</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>CBC</td>
<td>Low platelet count with normal hemoglobin/hematocrit and leukocyte count is evidence for the diagnosis of ITP. Anemia due to a nonimmune condition such as hemoglobinopathy or iron deficiency does not exclude ITP.</td>
</tr>
<tr>
<td>Peripheral blood smear</td>
<td>Exclude platelet clumping (pseudothrombocytopenia). Myeloid and erythroid morphology should be normal. Platelets should appear normal or may be large in size. Abnormal or immature leukocytes should be absent. The presence of schistocytes is associated with TTP and is evidence against ITP. The presence of polychromatophilia, poikilocytosis, and spherocytes suggests hemolytic anemia. Nucleated erythrocytes should be absent.</td>
</tr>
<tr>
<td>Bone marrow aspiration</td>
<td>Bone marrow aspiration and biopsy should be done to exclude other causes of thrombocytopenia, not to confirm the diagnosis of ITP. Typically, bone marrow examinations in patients with ITP show normal or increased numbers of megakaryocytes, normal myeloid and erythroid morphology, and no extrinsic cells.</td>
</tr>
<tr>
<td>HIV antibodies</td>
<td>Indicated to identify patients with HIV-associated ITP</td>
</tr>
<tr>
<td>HCV antibodies</td>
<td>Indicated to identify patients with HCV-associated ITP</td>
</tr>
<tr>
<td>PT/PTT</td>
<td>Coagulation testing is not recommended for routine diagnosis. However, an abnormal PT or PTT is evidence against ITP. The presence of thrombocytopenia and coagulopathy is associated with disseminated intravascular coagulation, or may be seen in the antiphospholipid antibody syndrome.</td>
</tr>
<tr>
<td>Thyroid function test</td>
<td>Hypo- or hyperthyroidism can be associated with ITP and should be excluded in patients for whom splenectomy is being considered.</td>
</tr>
<tr>
<td>ANA and other serologic tests</td>
<td>Consider ANA, ESR, and other serologic tests such as rheumatoid factor, complement levels, and anti-DNA, in patients with rash, synovitis, arthralgias, or other signs of rheumatologic disease, which may be secondary causes of ITP.</td>
</tr>
<tr>
<td>13C urea breath test or fecal antigen test</td>
<td>H. pylori eradication with antibiotics and a proton-pump inhibitor in patients with a positive 13C urea breath test or fecal antigen test has been shown to induce platelet recovery in some patients with ITP. The effect is mostly limited to certain countries, including Japan.</td>
</tr>
</tbody>
</table>

ANA = antinuclear antibody; CBC = complete blood count; DNA = deoxyribonucleic acid; ESR = erythrocyte sedimentation rate; HCV = hepatitis C virus; HIV = human immunodeficiency virus; ITP = immune thrombocytopenia; PT = plasma thromboplastin; PTT = partial thromboplastin time.
## Differential Diagnosis of Primary Immune Thrombocytopenia

<table>
<thead>
<tr>
<th>Disease</th>
<th>Characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary ITP</td>
<td>Primary ITP is a diagnosis of exclusion. Use history, physical exam and laboratory testing to rule out secondary causes of thrombocytopenia&lt;br&gt;The American Society of Hematology 2011 evidence-based practice guidelines are an excellent resource (1)</td>
</tr>
<tr>
<td>Pseudothrombocytopenia</td>
<td>In vitro clumping of platelets caused by EDTA-dependent agglutinins leads to falsely decreased platelet counts&lt;br&gt;Excluded by examination of peripheral blood smear and may require obtaining a platelet count in citrate (14)</td>
</tr>
<tr>
<td>Drug-induced thrombocytopenia</td>
<td>Many drugs have been implicated in thrombocytopenia, including heparin, beta lactams, sulfonamides, quinidine, quinine, abciximab, and Aggrenox (a fixed dose combination of aspirin and dipyridamole); alcohol also may lead to thrombocytopenia&lt;br&gt;Heparin-induced thrombocytopenia may be associated with thrombosis</td>
</tr>
<tr>
<td>Chronic liver disease</td>
<td>Portal hypertension can lead to splenic sequestration of platelets with resultant thrombocytopenia</td>
</tr>
<tr>
<td>Thrombotic thrombocytopenic purpura/HUS</td>
<td>TTP is characterized by thrombocytopenia, fever, microangiopathic hemolytic anemia, neurologic symptoms, and renal disease. HUS is characterized by thrombocytopenia, microangiopathic hemolytic anemia, and renal disease&lt;br&gt;Characterized by thrombocytopenia and the presence of schistocytes on peripheral blood smear</td>
</tr>
<tr>
<td>Disseminated intravascular coagulation</td>
<td>Coagulopathy characterized by an elevated prothrombin time and activated partial thromboplastin time, low fibrinogen, and thrombocytopenia</td>
</tr>
<tr>
<td>HELLP syndrome</td>
<td>Thrombocytopenia associated with elevated liver enzymes and hypertension in late pregnancy</td>
</tr>
<tr>
<td>Chronic lymphocytic leukemia</td>
<td>ITP may be a secondary complication of chronic lymphocytic leukemia; alternatively, thrombocytopenia in the setting of chronic lymphocytic leukemia may be nonimmune due to disease progression</td>
</tr>
<tr>
<td>Myelophthisis</td>
<td>Thrombocytopenia may be a manifestation of myelophthisis due to lymphoma, metastatic cancer, or granulomatous disease of the bone marrow</td>
</tr>
<tr>
<td>Infection</td>
<td>Thrombocytopenia is seen in HIV, hepatitis B and C, EBV, rubella, and other infections</td>
</tr>
<tr>
<td>Congenital thrombocytopenias</td>
<td>While rare, these conditions should be considered in younger patients with persistent thrombocytopenia and affected family members. May be accompanied by skeletal abnormalities&lt;br&gt;Includes Fanconi syndrome, Wiskott-Aldrich syndrome, thrombocytopenia with absent radius, and autosomal dominant macrothrombocytopenic disorders associated with MYH-9 mutations</td>
</tr>
</tbody>
</table>

EBV = Epstein-Barr virus; EDTA = ethylene diamine tetra-acetic acid; HELLP = hemolysis, elevated liver enzymes, and low platelet (count); HIV = human immunodeficiency virus; HUS = hemolytic-uremic syndrome; ITP = immune thrombocytopenia; TTP = thrombotic thrombocytopenic purpura.
# Drug Treatment for Primary Immune Thrombocytopenia

<table>
<thead>
<tr>
<th>Drug or Drug Class</th>
<th>Dosing</th>
<th>Side Effects</th>
<th>Precautions</th>
<th>Clinical Use</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Corticosteroids</strong></td>
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<tr>
<td>Prednisone</td>
<td>1-2 mg/kg qd. If platelet count normalizes over 1-2 weeks, taper by 5-10 mg/week</td>
<td>Long-term use can result in: HPA suppression, immuno-suppression, hypertension, adverse neurologic effects, glucose intolerance, weight gain, myopathy, glaucoma, osteoporosis</td>
<td>Use if platelets are &lt;20-30 x 10^9 and/or there is purpura or other bleeding</td>
<td></td>
</tr>
<tr>
<td>Dexamethasone</td>
<td>PO: 40 mg daily for 4 days</td>
<td>GI symptoms, flushing, diaphoresis, chills, wheezing, hypotension, hypersensitivity, injection site reactions. Rare: transfusion-related acute lung injury</td>
<td>Remote risk of transmission of viral infection. Caution with elderly</td>
<td>Alternative to prednisone</td>
</tr>
<tr>
<td><strong>Immune globulin</strong></td>
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<tr>
<td>Intravenous immune globulin, IVIG (Gammar-P I.V., Carimune NF, Gammagard S/D)</td>
<td>1-2 g/kg IV (administered in divided doses given over 2-5 days)</td>
<td>Thrombotic events, coagulation adverse events, hemolytic anemia, aseptic meningitis syndrome</td>
<td>Risk of nephrotoxicity and death. Reduce dose, concentration, and/or rate in patients at risk for renal failure</td>
<td>For patients: refractory to corticosteroids or with severe bleeding or for use prior to surgery</td>
</tr>
<tr>
<td>Rh(D) Immune Globulin, RhIG (WinRho SDF)</td>
<td>50-75 μg/kg IV as a single dose</td>
<td>Intravascular hemolysis leading to death; severe anemia, nephrotoxicity, DIC</td>
<td></td>
<td>For Rh(+) patients who have not had splenectomy</td>
</tr>
<tr>
<td><strong>Agents for refractory ITP</strong></td>
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<tr>
<td>Thrombopoietin receptor agonists</td>
<td></td>
<td>Thrombotic complications, myalgia, paresthesias</td>
<td>Monitor CBC with differential weekly during dose adjustment, then monthly</td>
<td>Can improve platelet count but do not induce true remission</td>
</tr>
<tr>
<td>Eltrombopag (Promacta)</td>
<td>50 mg PO qd. Maximum total daily dose 75 mg. Take 1 hour before or 2 hours after a meal. Do not take within 4 hours of: antacids, dairy, mineral supplements</td>
<td>Vomiting, diarrhea, infection, rash</td>
<td>Hepatotoxicity. Measure LFTs at baseline, every 2 weeks during dose adjustment, then monthly. Decrease initial dose with: hepatic disease, East Asian ancestry</td>
<td></td>
</tr>
<tr>
<td>Romiplostim (Nplate)</td>
<td>1 μg/kg SC once weekly. Maximum weekly dose 10 μg/kg</td>
<td>Arthralgia, dizziness, insomnia, extremity pain, abdominal pain, dyspepsia</td>
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<tr>
<td><strong>Anti-CD20 monoclonal antibody</strong></td>
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<tr>
<td>Rituximab (Rituxan)</td>
<td>375 mg/m² IV weekly for 4 doses</td>
<td>Hematologic toxicity, risk of: infection, bleeding, malignancy. Hypotension, nephrotoxicity, vomiting, abdominal pain, GI perforation, peripheral neuropathy</td>
<td>Fatal infusion reactions, severe mucocutaneous reactions, PML, HBV reactivation. Avoid with pregnancy</td>
<td>Can induce remission or delay splenectomy</td>
</tr>
<tr>
<td><strong>Androgen</strong></td>
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</tr>
<tr>
<td>Drug</td>
<td>Dose</td>
<td>Adverse Effects</td>
<td>Notes</td>
<td></td>
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<td>-------------------------------</td>
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<tr>
<td>Danazol</td>
<td>200 mg qid</td>
<td>Androgenic and hypoestrogenic effects, GI side effects, hypercholesterolemia, allergic reactions, CNS side effects, hematologic toxicity, interstitial pneumonitis</td>
<td>Avoid with pregnancy. Thrombotic events, benign intracranial hypertension. Peliosis hepatitis and benign hepatic adenoma with long term use. Avoid with: severe hepatic or cardiac disease, CrCl&lt;30, acute intermittent porphyria. Caution with elderly. Inhibits CYP3A4</td>
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</tr>
<tr>
<td><strong>Immunosuppressants</strong></td>
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<tr>
<td>Azathioprine (Imuran, Azasan)</td>
<td>150 mg qd</td>
<td>Hepatotoxicity</td>
<td>Increased risk of malignancy. Caution with: CKD, thiopurine methyltransferase deficiency</td>
<td></td>
</tr>
<tr>
<td>Cyclosporine (Gengraf, Sandimmune, Neoral)</td>
<td>1-1.5 mg/kg bid</td>
<td>Nephrotoxicity, hyperkalemia, hyperuricemia, hypertension, hepatotoxicity, hypercholesterolemia, seizures, hirsutism, hypertrichosis, gingival hyperplasia, gynecomastia</td>
<td>For use by experienced physicians. Immuno-suppression and risk of infection. Formulations are not interchangeable. Monitor blood levels. Avoid excess sunlight. Caution with hepatic disease. Substrate of CYP3A, substrate and inhibitor of P-gp</td>
<td></td>
</tr>
<tr>
<td>Mycophenolate mofetil (CellCept)</td>
<td>1.5-2 g qd</td>
<td>GI side effects, nephrotoxicity, respiratory adverse events, ophthalmic adverse events, asthenia, insomnia, paresthesias</td>
<td>Administer by experienced personnel in an equipped facility. Immuno-suppression and risk of infection. Risk of pregnancy loss and teratogenicity. Caution with: hepatic disease, CrCl&lt;25</td>
<td></td>
</tr>
<tr>
<td><strong>Cytoreductive agents</strong></td>
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<tr>
<td>Cytosporophamide</td>
<td>PO: 2 mg/kg qd. High-dose IV: 1-1.5 g/m² every 4 weeks</td>
<td>Hemorrhagic cystitis, infertility, SIADH, cardiotoxicity, interstitial pneumonitis, anaphylaxis, alopecia, vomiting</td>
<td>Consider dose reduction if CrCl&lt;55</td>
<td></td>
</tr>
<tr>
<td><strong>Vinca alkaloids</strong></td>
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<tr>
<td>Vinblastine</td>
<td>IV: 5-10 mg weekly</td>
<td>Myelosuppression is dose-limiting. Neurotoxicity less common than with vincristine. Mild alopecia, peripheral vasoconstriction</td>
<td>IV use only, must not be given intrathecally. Severe granulocytopenia, avoid extravasation. Decrease dose if total bilirubin is elevated. Substrates of CYP3A4 and P-gp</td>
<td></td>
</tr>
<tr>
<td>Vincristine</td>
<td>IV: 1-2 mg weekly</td>
<td>Neurotoxicity is dose-limiting. Severe constipation, alopecia, rash, hypotension, urinary retention</td>
<td>For patients refractory to multiple other therapies</td>
<td></td>
</tr>
<tr>
<td><strong>Other</strong></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Colchicine (Colcrys)</td>
<td>0.6 mg tid</td>
<td>GI side effects, myelosuppression, myopathy, peripheral neuropathy,</td>
<td>Avoid if taking a moderate-strong CYP3A4 inhibitor or P-gp inhibitor with</td>
<td></td>
</tr>
</tbody>
</table>
### Primary Immune Thrombocytopenia

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>Adverse Effects</th>
<th>Precautions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dapsone</td>
<td>75 mg qd</td>
<td>Rhabdomyolysis, nephrotoxicity, elevated hepatic enzymes</td>
<td>Hepatic disease or CKD. Decrease dose if taking a moderate-strong CYP3A4 inhibitor or P-gp inhibitor. Decrease dose with CKD. Caution with hepatic disease. Avoid alcohol.</td>
</tr>
</tbody>
</table>

- **75 mg qd**
- **Hemolytic anemia, methemoglobinemia, toxic hepatitis, jaundice, nephrotoxicity, vomiting**
- **Monitor hepatic function. Caution with: G6PD deficiency, sulfonamide allergy. Substrate of CYP3A4**

*Substrate of CYP3A4 = first-line agent; □ = black box warning; bid = twice daily; CBC = complete blood count; CKD = chronic kidney disease; CNS = central nervous system; CrCl = creatinine clearance; CV = cardiovascular; CYP = cytochrome P450 isoenzyme; DIC = disseminated intravascular coagulation; ECG = electrocardiogram; G6PD = glucose-6-phosphate dehydrogenase; GI = gastrointestinal; HPA = hypothalamic-pituitary-adrenal; IM = intramuscular; IV = intravenous; LFT = liver function test; P-gp = P-glycoprotein; PML = progressive multifocal leukoencephalopathy; PO = oral; prn = as needed; q12hr = every 12 hours; qd = once daily; qid = four times daily; SC = subcutaneous; SCr = serum creatinine; SIADH = syndrome of inappropriate antidiuretic hormone secretion; tid = three times daily.*

PIER provides key prescribing information for practitioners but is not intended to be a source of comprehensive drug information.
Pseudothrombocytopenia

The peripheral blood smear shows platelet clumping, which suggests pseudothrombocytopenia. Pseudothrombocytopenia is a laboratory artifact in which platelets drawn into an EDTA-anticoagulated test tube clump and fail to be counted accurately by the automated counter, resulting in a spuriously low platelet count.
**Petechia due to Thrombocytopenia**

A petechia is a round, discrete, hemorrhagic area typically less than 2 mm in diameter that is caused by thrombocytopenia. As the lesion ages and the hemoglobin is metabolized, the color changes from bright red to green to yellow and then fades. Petechiae do not blanch with pressure and are flat and nontender.
Normal Platelets on Peripheral Blood Smear

Platelets are small purple anuclear cells. Seven platelets per 100-power field is normal and less than seven suggests thrombocytopenia.
Giant Platelet on Peripheral Blood Smear

Giant platelets suggest an increased marrow response secondary to a destructive process as might be seen with immune thrombocytopenic purpura. If associated with fragmented erythrocytes, giant platelets might suggest the presence of thrombotic, thrombocytopenic purpura.