CME CREDIT

Idiopathic thrombocytopenic purpura: Guidance amid uncertainty

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ABSTRACT

Clinical guidelines for treating ITP are based on the consensus of an expert panel, as randomized trials are lacking. Newer genetically engineered treatments hold promise but await definitive study.

"Science is what you know, philosophy is what you don't know."

—BERTRAND RUSSELL

Randomized studies of ITP in adults are lacking

WHAT IS THE BEST way to treat idiopathic thrombocytopenic purpura (ITP)? It seems like a simple question about a relatively common condition. Yet when the American Society of Hematology set out to write clinical practice guidelines for treating ITP, they found little solid evidence favoring one treatment over another—the available literature consists almost entirely of retrospective studies. Randomized studies of ITP in adults are lacking.

As a result, the society had to base its guidelines for ITP on the consensus of an 11-member expert panel, using a weighted polling system devised by the RAND corporation.[1,2] This article briefly reviews the key recommendations and discusses potential new therapies and areas for research.

WHAT IS ITP?

In ITP, also known as primary immune or autoimmune thrombocytopenic purpura, platelets become coated with immunoglobulin (IgG) and are destroyed in the spleen, liver, and reticuloendothelial system.[3] The prevalence in both adults and children ranges from 1 to 13 per 100,000 persons. The typical adult patient is a woman between 20 and 30 years old who presents with purpura and a low platelet count.

The American Society of Hematology panel defined ITP as isolated thrombocytopenia (a low platelet count with otherwise normal results on the complete blood count and peripheral blood smear) in a patient with no clinically apparent conditions or factors that can cause thrombocytopenia. (A normal platelet count in adults is 150 to 400 × 10^9/L.)

The principal cause of death in ITP is intracranial hemorrhage, although this has become rare since better supportive care techniques have been developed. The principal cause of morbidity is treatment-related toxicity.

HOW TO DIAGNOSE ITP

Patient history: Is a low platelet count really ITP?

When a patient presents with a low platelet count, try to identify a cause, which would rule out ITP. In particular, ask about:

- **Drugs** that can stimulate the immune system to destroy platelets (eg, heparin, quinidine, sulfa drugs) or oral antidiabetic drugs, gold salts, and rifampin, or drugs that can exacerbate bleeding (eg, aspirin)
- **Alcohol use,** which can cause thrombocytopenia due to platelet pooling from congestive splenomegaly (Of note: In addition to alcohol, tonic water, which contains quinine and is used in mixed drinks such as gin and tonic, can cause quinine purpura.)
- **Environmental agents,** such as a new perfume or detergent that may have stimulated an immunologic reaction in the patient
- **Systemic symptoms,** especially of

TABLE 1

Initial treatment options for adults with idiopathic thrombocytopenic purpura, according to an expert panel

PLATELET COUNT AND BLEEDING STATUS*	PANEL IN AGREEMENT	APPROPRIATENESS UNCERTAIN
Platelet count 50–100 × 10^9/L		
Asymptomatic	Observation	NR†
Minor purpura	Observation	NR
Mucous membrane bleeding	NR	Observation, glucocorticoids, hospitalization
Platelet count 30–50 × 10^9/L		
Asymptomatic	NR	Glucocorticoids
Minor purpura	NR	Glucocorticoids
Mucous membrane bleeding	Glucocorticoids‡	Hospitalization, IV IgG§
Severe bleeding	Glucocorticoids, IV IgG, hospitalization	
Platelet count 20–30 × 10^9/L		
Asymptomatic	NR	Glucocorticoids, IV IgG
Minor purpura	Glucocorticoids	IV IgG
Mucous membrane bleeding	Glucocorticoids	Hospitalization, IV IgG
Severe bleeding	IV IgG, glucocorticoids, hospitalization	Splenectomy
Platelet count 10–20 × 10^9/L		
Asymptomatic	Glucocorticoids	Hospitalization, IV IgG
Minor purpura	Glucocorticoids	Hospitalization, IV IgG
Mucous membrane bleeding	Glucocorticoids, hospitalization	IV Ig
Severe bleeding	IV IgG, glucocorticoids hospitalization	Splenectomy
Platelet count < 10 × 10^9/L		
Asymptomatic	Glucocorticoids	IV IgG, hospitalization
Minor purpura	Glucocorticoids	IV IgG, hospitalization
Mucous membrane bleeding	Glucocorticoids, hospitalization	IV IgG
Severe bleeding	IV IgG, glucocorticoids, hospitalization	Splenectomy

*Mucous membrane bleeding includes vaginal bleeding and other blood loss requiring clinical intervention; severe bleeding includes life-threatening bleeding; "Severe" category not included for platelet counts of 50 to 100 × 10^3 per mm^3 (50 to 100 × 10^9 per L) because severe bleeding in such patients is unlikely to be caused by ITP
†No recommendation
‡Prednisone 1 to 2 mg/kg/day or an equivalent drug
§Intravenous immune globulin 1 to 2 g/kg, for 1 to 5 days

SOURCE: ADAPTED FROM AMERICAN SOCIETY OF HEMATOLOGY ITP PRACTICE GUIDELINE PANEL, AM FAM PHYSICIAN 1996; 54:2437–2447.

Do not automatically order a bone marrow aspiration

recent viral illness or symptoms of an autoimmune disorder (eg, arthralgias, skin rash, alopecia, venous thrombosis)

- **Recent immunizations** or blood transfusions
- **A family history** of thrombocytopenia
- **Risk factors for HIV,** or recurrent infections (which might suggest immunodeficiency)
- **Bleeding history.** Ask about the current bleeding: its type, severity, and duration. Also ask about past episodes of bleeding. Did the patient ever have bleeding problems before, especially during pregnancy or surgery?

Does he or she have conditions that may increase the risk of bleeding, such as gastrointestinal, central nervous system, or urologic disease? If a woman, is she pregnant or trying to become pregnant?

Physical examination: Search for bleeding and signs of infection

During the physical exam, the physician should check for retinal hemorrhage, and also for enlargement of the liver, spleen, and lymph nodes. Splenomegaly provides evidence against ITP; hepatomegaly or lymphadenopathy may suggest lymphoproliferative, autoimmune, or infectious diseases.

Peripheral blood smear

In ITP, the platelet count is low, but the platelets are normal in size or slightly larger than normal. The red blood cells and white blood cells should be normal in morphology. Findings incompatible with ITP include predominately giant platelets, poikilocytosis, schistocytosis, polychromatophilia, macrocytes, nucleated red cells, and leukocytosis or leukopenia with immature or abnormal cells.

Is bone marrow aspiration necessary?

In the past, bone marrow aspiration was routinely ordered whenever a patient's platelet count dropped to 130 × 10^9/L or lower. However, the American Society of Hematology panel found no evidence that such testing is routinely necessary. The panel did say that bone marrow aspiration is appropriate for patients older than 60 to rule out myelodysplasia, and for patients being considered for splenectomy. Also, if anything abnormal is detected on the peripheral blood smear (besides thrombocytopenia), a bone marrow examination is warranted.

TREATMENT

In adults, the American Society of Hematology panel favored observation, corticosteroids, or intravenous IgG as initial treatment, depending on the platelet count and the severity of bleeding (TABLE 1). In general, the lower the platelet count and the more severe the bleeding, the greater the need for intervention.

Unlike adults, most children recover spontaneously, making watchful waiting a better option than in adults. Like adults, children need active treatment if the bleeding is severe or the platelet count is extremely low, but the American Society of Hematology panel was more divided in its opinions about where these cutpoints should be in children than in adults. In particular, many pediatric hematologists complained that the guidelines favored the use of IV IgG in children with ITP. This continues to be an area of controversy.

When is splenectomy appropriate?

The panel voted that splenectomy is of uncertain appropriateness as initial therapy, but is appropriate if bleeding continues and if the platelet count remains below 30 × 10^9/L after 4 to 6 weeks of treatment with glucocorticoids. And in fact, most adult patients either do not have a response to glucocorticoids, or experience a relapse after the glucocorticoids are tapered and stopped, and therefore eventually need a splenectomy.

Refractory ITP

For patients who have active bleeding and platelet counts less than 30 × 10^9/L after treatment with glucocorticoids and splenectomy, the options include intravenous IgG, corticosteroids, accessory splenectomy, or no additional treatment.[4]

ITP in pregnancy

ITP is often indistinguishable from gestational thrombocytopenia in pregnant women, making diagnosis difficult. No treatment is required for pregnant women who have ITP and platelet counts greater than 50 × 10^9/L and who are not bleeding. However, treatment is necessary for pregnant women with platelet counts less than 10 × 10^9/L, and for those with platelet counts of 10 to 30 × 10^9/L who are in the second or third trimester or are bleeding. These therapies include glucocorticoids and IV IgG. Splenectomy is appropriate for pregnant women in their second trimester who have platelet counts less than 10 × 10^9/L, who are bleeding, and for whom glucocorticoids and IV IgG have failed.

Splenectomy is not indicated as initial therapy for patients with minor purpura or no bleeding

FUTURE ITP TREATMENTS

Several new treatments for ITP are in development.

Thrombopoietin (megakaryocyte growth and development factor) has been tested in patients undergoing cancer chemotherapy, in whom it speeds the recovery of the platelet count.[5]

Anti-CD40 ligand blocks interactions of T lymphocytes with other cells, inhibits B lymphocyte production of antibodies to proteins, and blocks migration of B lymphocytes to germinal centers.[6] Preliminary studies indicate that this agent suppresses the production of antibodies that destroy platelets, but patients retain the ability to fight infection.

Anti-D, known by the brand name WinRho, directly binds to red blood cells and may prevent the need for splenectomy in patients with newly diagnosed ITP.[7] It was recently approved by the FDA for treating ITP in patients who still have a spleen.

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