Adult Idiopathic Thrombocytopenic Purpura (ITP): A Review of the Disease

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Introduction

Idiopathic, or immune, thrombocytopenic purpura (ITP) is an autoimmune disorder usually characterized by increased platelet destruction and suboptimal platelet production. ITP results in diminished platelet levels and an increased risk for minor and major bleeding events. Approximately 200,000 individuals in the United States have ITP. New adult cases of ITP occur at an annual rate of approximately 50 per 1 million individuals; about 25% to 30% of these patients develop chronic ITP that goes on to become refractory to treatment. The incidence of ITP increases with age, as does the severity of the condition. ITP is more common in women than in men, with a female-to-male ratio of 1.2 to 1.9:1, although that difference virtually disappears in older patients.

This special report reviews the underlying mechanisms of platelet development in hematopoiesis and the key role of thrombopoietin (TPO); the pathophysiology, signs, and symptoms of ITP and how platelet development is impaired and platelets are destroyed; the potentially severe consequences associated with the condition; and the current treatments available. Additionally, it examines the pharmacist’s role in ensuring the appropriate, effective, and safe use of medications needed by patients with ITP.
Self-assessment: True or False

The following questions are designed to test the reader’s knowledge of ITP.

1. Endogenous thrombopoietin plays a key role in platelet development.

2. Gingival bleeding may be an early sign of thrombocytopenia.

3. Most patients with ITP who have failed to respond to corticosteroids achieve a sustained increase in platelet count with intravenous immunoglobulins (IVIG), anti-D therapy, or splenectomy.

4. Splenectomy is a procedure typically used in patients who have not received other treatments for ITP.

(Answer key on page 8)

Basic Mechanisms

The molecular biology of platelet formation is complex, involving multiple hematopoietic factors and signaling pathways. The endogenous growth factor TPO plays an important role in this process. Synthesized primarily in the liver, kidneys, and bone marrow, TPO stimulates the proliferation and maturation of these precursors into megakaryocytes, the large hematopoietic cells that act as incubators for platelet development. Preclinical studies have shown that other cytokines, including interleukins 1, 3, 6, and 11 and granulocyte-macrophage colony-stimulating factor, also play roles in thrombopoiesis.

Once platelet formation occurs, there are many complex factors that can influence the number of platelets available for thrombopoiesis. As the number of platelets in the blood increases, for example, more TPO is bound to the TPO receptor on circulating platelets; the result is less free TPO to trigger thrombopoiesis. The converse is also true: Lower platelet levels mean more free TPO available for binding to megakaryocytic precursor cells, leading to increased platelet production.

In otherwise healthy adults, platelet counts can range from 150,000 to 450,000/mcL. In ITP, this balance is disrupted. Two mechanisms may account for the disruption: increased platelet destruction and impaired platelet production. In ITP, platelet destruction is the main factor, but it is now realized that impaired production is also involved. The body mounts an autoimmune attack and autoantibodies bind to platelets, causing their sequestration and destruction in the spleen. TPO bound to the platelets is also destroyed.

The following mechanisms result in even fewer platelets being produced to replace those lost due to destruction in the spleen: Endogenous TPO (eTPO) is bound by platelets resulting in lower concentrations of eTPO in the blood. There is less eTPO available to stimulate platelet production by the megakaryocytes in the bone marrow. Autoantibody binding to the megakaryocytes causes some to undergo apoptosis. There are fewer megakaryocytes available to produce platelets. eTPO also is lost when bound to apoptotic megakaryocytes.

The etiology of ITP is not completely understood. It has been postulated that in a person with ITP, the immune system generates autoantibodies that coat circulating platelets, marking them for destruction by phagocytes primarily in the spleen and liver. Other mechanisms that have been hypothesized include T cell–mediated cytotoxicity and suppression of megakaryocyte production by antibodies. This condition may be acute, resolving by itself within 6 months (although this is rare in adult patients with ITP), or it may persist.

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To diagnose ITP, physicians must first exclude other reasons that patients— who may be asymptomatic on presentation or exhibit signs of mucocutaneous bleeding such as petechiae and bruising— have a low platelet count. The recommended step-by-step approach was fully described in the ITP practice guideline developed more than a decade ago by an American Society of Hematology (ASH) panel. In 2005, Cines and Busk described a similar approach that they take in their own clinical practice.

According to the ASH guideline, a diagnosis of ITP is based mainly on history and physical examination (Table 1) as well as complete blood cell count and examination of a peripheral blood smear. These initial diagnostic components should eliminate some of the potential causes of a low platelet count, including exposure to certain drugs, food, alcohol, and other substances; pseudothrombocytopenia; congenital thrombocytopenia; and chronic liver disease. Patients’ whose histories may suggest risk for HIV infection should be tested for this disease. The ASH treatment guideline recommends that a bone marrow aspirate be evaluated routinely in patients older than 50.
age 60; those for whom splenectomy is being considered; and those who have not responded to treatment with corticosteroids, splenectomy, or other modalities.

Morbidity and Mortality

The risk, as well as the seriousness of bleeding events, increases in inverse proportion to the gradual reduction in platelet counts. At levels above 50,000/mcL, thrombocytopenia is usually diagnosed incidentally, as the result of a routine blood test. When platelet counts fall below that mark, the risk for symptoms of bleeding increases, with specific symptoms developing based on the range of platelet counts present. Patients with platelet levels between 30,000 and 50,000/mcL, for example, may experience excessive bruising with minor trauma; when platelets range between 10,000 and 30,000/mcL, petechiae or ecchymoses can occur spontaneously. When the platelet count falls to 10,000/mcL or lower, the risk for internal hemorrhage is greatly magnified.

Options for the Treatment of ITP

Numerous factors need to be considered when deciding whether to treat a patient with ITP (Table 2). The treatment that a clinician selects partly depends on platelet count and severity of illness at presentation. For example, patients presenting with very low platelet levels (<10,000/mcL) and hemorrhage require emergency care, which typically involves platelet transfusion, IVIG (1 g/kg per day for 2-3 days), or methylprednisolone (1 g per day for 3 days).

Current treatment approaches are primarily aimed at preventing or minimizing platelet destruction. Once it has been determined that a patient does require therapy, clinicians have limited options. The main therapies used for the treatment of ITP (although not all are FDA-approved) are outlined below.

Corticosteroids

Corticosteroids are approved by the FDA for use in the initial management of adult patients with ITP. Corticosteroids are immunosuppressants that target B cells, limiting their ability to synthesize platelet-targeting antibodies. According to the ASH practice guideline, consistent evidence has shown that the use of corticosteroids can result in early, but mostly transient, increases in platelet count. The ASH guideline asserts that there is little evidence on which to base recommendations for dosing, but it does offer recommendations based on opinions of the members of the expert panel whose judgment was used in creating the document. The consensus is that oral corticosteroid therapy (prednisone, 1-2 mg/kg per day) is appropriate as initial therapy for patients with a platelet count below 30,000/mcL, including asymptomatic patients, those with minor purpura, and those with significant mucous membrane or vaginal bleeding. The guideline also states that steroid therapy is appropriate in patients with a platelet count of 30,000 to 50,000/mcL who have clinically significant bleeding and for all patients with severe, life-threatening bleeding, regardless of the platelet level. How long to use corticosteroids as initial therapy and how fast to taper are subject to debate, with opinions varying from 2 to 6 weeks.

Depending on the intensity of this initial therapy and how long it is continued, 50% to 75% of patients respond, typically within 3 weeks. If platelet levels remain below 20,000/mcL or if there is another reason for seeking a more rapid response, oral corticosteroid therapy is sometimes supplemented with other therapies, which could include IVIG (1 g/kg per day for 1-2 days) or intravenous (I.V.) methylprednisolone (1 g).

Table 1. Diagnosing ITP in Adults

<table>
<thead>
<tr>
<th>History</th>
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<tbody>
<tr>
<td>Symptom, type, severity, and duration of bleeding</td>
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<tr>
<td>Hemostasis with prior surgeries, pregnancies</td>
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<tr>
<td>Weight loss, fever, and headache</td>
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<tr>
<td>Symptoms of autoimmune disorders (eg, arthralgias, skin rash, alopecia, and venous thrombosis)</td>
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<tr>
<td>Risk factors for HIV infection</td>
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<tr>
<td>Pregnancy status</td>
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<tr>
<td>Medications: heparin, alcohol, quinidine/quinine, sulfonamides (may cause thrombocytopenia); and aspirin (may exacerbate bleeding)</td>
</tr>
<tr>
<td>Transfusion history</td>
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<tr>
<td>Family history of thrombocytopenia, including bleeding and autoimmune disorders</td>
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<tr>
<td>Comorbidities that may increase risk for bleeding, such as GI, CNS, and urologic disease</td>
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<tr>
<td>Vigorous, potentially traumatic physical activities</td>
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</tbody>
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<table>
<thead>
<tr>
<th>Physical Examination</th>
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<tbody>
<tr>
<td>Signs, type, and severity of bleeding</td>
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<tr>
<td>Liver, spleen, and lymph nodes; jaundice and other stigmata of liver disease</td>
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<tr>
<td>Evidence of infection, particularly bacteremia or HIV infection</td>
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<tr>
<td>Evidence of autoimmune disease (eg, arthritis, goiter, nephritis, or cutaneous vasculitis)</td>
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<tr>
<td>Evidence of thrombosis</td>
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<tr>
<td>Neurologic function</td>
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<tr>
<td>Skeletal anomalies</td>
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</tbody>
</table>

Adapted from reference 18 (Blood. 1996;88:3-40)
**Table 2. Factors That Should Be Considered in Deciding When To Treat Patients With Idiopathic Thrombocytopenic Purpura**

<table>
<thead>
<tr>
<th>Additional risk factors for bleeding</th>
<th>Advanced age</th>
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<tbody>
<tr>
<td>Adverse effects of treatment</td>
<td>Alcoholism</td>
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<tr>
<td>Aneurysms</td>
<td></td>
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<tr>
<td>Chronic liver diseases</td>
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<td>Depressed platelet count</td>
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<tr>
<td>Fever</td>
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<td>History of peptic ulcer disease</td>
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<tr>
<td>Infections</td>
<td></td>
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<tr>
<td>Lifestyle (participation in activities that predispose to trauma)</td>
<td></td>
</tr>
<tr>
<td>Presence of active bleeding</td>
<td>Presence of active bleeding</td>
</tr>
<tr>
<td>Untreated or poorly controlled hypertension</td>
<td></td>
</tr>
<tr>
<td>Uremia</td>
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</table>

Rapid and durable responses have been reported in patients receiving oral dexamethasone (40 mg per day for 4 days per month), but whether that treatment increases the long-term response in comparison with prednisone requires further study. Adverse effects associated with long-term corticosteroid use include fluid and electrolyte disturbances, cardiovascular disorders, myopathy, osteoporosis, weight gain, hyperglycemia, glaucoma, and gastrointestinal disorders. Additionally, steroids can mask signs of infection or the development of new infections, which may be mild or severe. It is important to note that the adverse reactions to corticosteroids outlined above are largely based on studies of patients with a variety of underlying diseases; ITP-specific data are lacking. However, one recent case study of a patient with ITP who developed a fatal aspergillosis lung infection after being treated with corticosteroids underscores the inherent risk (although fatalities are rare) of treating ITP patients with immune-suppressing medications.

**Intravenous Immunoglobulin**

Approved by the FDA for the treatment of adults with chronic ITP, IVIG is commonly used to stem internal bleeding when patients’ platelet count remains below 5,000/mcL despite corticosteroid therapy, or in patients with extensive or progressive purpura. Although the mechanism of action is not entirely clear, IVIG appears to block the crystallizable fragment (Fc) γ receptors of macrophages that recognize autoantibodies bound to platelets and thereby initiate platelet removal. IVIG has been shown to be effective in raising platelet counts in up to 85% of patients, with 65% achieving a count above 100,000/mcL. The response normally begins after 1 day of treatment but in most cases is transient—lasting 3 to 4 weeks before the platelet count retreats to pretreatment levels. Adverse effects of IVIG therapy are common but generally mild. They include headache, backache, nausea, and fever. Occasionally, headaches can be severe and occur in conjunction with nausea and vomiting, symptoms that mimic those of intracranial hemorrhage, and computed tomography may be needed to determine a diagnosis. Renal failure, pulmonary insufficiency, and thrombosis—which can lead to stroke and myocardial infarction—are among the serious adverse events that have been reported with the administration of IVIG.

Many of the milder adverse effects associated with infusion can be minimized by infusing the drug slowly over several hours. When a rapid increase in the platelet count is necessary before emergency surgery or to counter internal bleeding, IVIG is the agent of choice (1 g/kg per day for 2-3 days), along with methylprednisolone (1 g per day for 2-3 days) and an infusion of platelets at a level 2-fold to 3-fold higher than usual. The dosage recommended in the labeling for IVIG is 0.4 g/kg of body weight on 2 to 5 consecutive days.

**Rho(D) Immune Globulin Intravenous (Human)**

Although oral prednisone is used initially for most patients’ ITP, clinicians will substitute I.V. anti-D in Rh-positive and direct antoglobulin-negative patients who are unable to tolerate corticosteroids or in whom their use is contraindicated. Anti-D has been shown to be effective for increasing platelet count and reducing bleeding in nonsplenectomized Rh(D) positive adults with chronic ITP and is approved by the FDA for that indication. The dosage recommended in the labeling for the agent is 250 IU (50 mcg)/kg of body weight; the rate of infusion is 2 mL per 15 to 60 seconds. The response is predictably transient, with the expectation that platelet counts will return to baseline in 3 to 4 weeks. The mechanism of action is not completely understood but is thought to involve the formation of Rho(D) immunoglobulin–red blood cell complexes that are preferentially removed by the reticuloendothelial system, particularly the spleen, resulting in a blockade of Fc γ receptors and sparing antibody-coated platelets.
The evidence for the use of anti-D is limited. The agent was evaluated in 2 trials involving Rho(D)-positive, non-splenectomized adults. In the first trial, George et al sought to determine if the use of anti-D in adult patients with newly diagnosed ITP and a platelet count below 30,000/mcL might avoid or delay the need for splenectomy in comparison with routine care (ie, glucocorticoid therapy followed by splenectomy). The investigators found that splenectomy was performed in 14 of 33 (42%) patients in the anti-D group and 14 of 37 (38%) in the routine care group (absolute risk reduction, 4.6% in favor of routine care; 95% confidence interval, -18.4% to 27.6%).

The investigators noted, however, that splenectomy was performed prematurely and not according to protocol in 11 of the 14 patients receiving anti-D. In the routine care group, the median time to splenectomy was 36 days (range, 9-78 days) and 112 days (range, 19-558 days) in the anti-D group. No major bleeding episodes occurred in either group during the study period. Eleven patients in the routine care group and 12 in the anti-D group had minor bleeding events. Following infusion of anti-D, 7 of 32 patients had moderate or severe systemic symptoms (including fever, chills, nausea, vomiting and myalgia). Three patients who received anti-D experienced a decrease in hemoglobin of at least 3 g/dL. In 1 of the 3 patients, menorrhagia may have contributed to the decrease. Although 2 deaths occurred, neither was attributed to the study procedures or to ITP.

In the second study, Cooper et al also looked at whether the use of anti-D could avoid splenectomy in adult patients with ITP who had not responded to an initial course of steroids. Of the 28 patients evaluated during the study period, 12 (43%) were able to discontinue treatment, with their platelet level maintained above 30,000/mcL for more than 6 months; the condition of 6 of these patients continued to improve after treatment was discontinued, with their platelet level maintained above 30,000/mcL; and 3 were in complete remission. A total of 71% avoided splenectomy through the study period; those who continued receiving anti-D received therapy less often. The researchers concluded that a splenectomy may not be immediately necessary in all adults with recently diagnosed ITP who do not go into remission with an initial course of steroids.

**Splenectomy**

Patients in whom initial therapy with corticosteroids, IVIG, or anti-D has failed usually undergo surgery to remove the spleen. Numerous studies have demonstrated that splenectomy produces a response in approximately two-thirds of patients, usually within several days. In fact, Cines and Bussel describe splenectomy as “the single best option to convert a patient with ITP into a ‘nonpatient,’ that is, one who is unlikely to need frequent monitoring or intervention, and it minimizes interference with a normal lifestyle.” A recent literature review by Mikhail et al suggests that splenectomy is not always initially successful and does not provide a durable response in all patients. The review found that 12% of patients undergoing splenectomy do not achieve a platelet response, and 5% of patients relapse each year after undergoing the procedure. The 5-year failure rate after splenectomy was 32%.

Opinions vary on when and under what circumstances to perform a splenectomy. The ASH treatment guideline states that if steroid therapy has failed, splenectomy is appropriate in patients with (1) a diagnosis of ITP of at least 6 weeks’ duration, a platelet count below 10,000/mcL, and no symptoms of bleeding and (2) a diagnosis of at least 3 months’ duration who have had a temporary or incomplete response to primary treatment, have a platelet count below 30,000/mcL, and are or are not bleeding. The guideline also suggests a preoperative thyroid test be administered to rule out occult hyperthyroidism or hypothyroidism before elective splenectomy.

When splenectomy fails to produce the desired outcome, patients face the possibility of long-term treatment with corticosteroids and other therapies and a greatly heightened risk for morbidity and mortality if the disease proves to be refractory to treatment.

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Potentially life-threatening pneumococcal sepsis remains a risk for patients who have undergone removal of the spleen. The ASH panel supports recommendations from the Advisory Committee on Immunization Practices that patients undergoing elective splenectomy should be immunized with a polyvalent pneumococcal vaccine, Haemophilus influenzae type b vaccine, and quadrivalent meningococcal polysaccharide vaccine. To reduce the risk for bleeding during or following the operation, the ASH treatment guideline recommends preoperative prophylaxis with IVIG or oral steroid therapy in patients with a platelet count below 20,000/mcL. Additionally, laparoscopic splenectomy appears to be preferable to an open procedure, speeding recovery and shortening hospitalization. A laparoscopic procedure often can be performed, if necessary, without additional therapy in patients who have low platelet counts.

For the 30% to 40% of patients who do not respond to splenectomy or who relapse following the procedure, several treatment options exist. But there is some disagreement over...
the rate of true failure—that is, the proportion of splenectomized patients who continued to show no response even after follow-up therapy. McMillan et al followed 114 patients with ITP who failed to respond to splenectomy and who required additional therapy. Long-term follow-up data were available on 105 of these patients. After a mean of 11.9 years, 28.6% of the patients remained unresponsive to treatment. In Vianelli et al, the failure rate was relatively low (12%) after a mean follow-up of 57 months (4.8 years) post-splenectomy. But although the incidence of those treatment failures may be debated, McMillan et al makes it clear that there is a subpopulation of ITP patients with severe, resistant disease who experience significant morbidity and mortality.

**Rituximab**

Rituximab (Rituxan®, Genentech and Biogen Idec) is not approved in the United States for the treatment of ITP, but it has been used investigational for the treatment of the estimated 25% to 30% of adult patients with severe ITP who are refractory to conventional therapies. This monoclonal antibody therapy, which is indicated for non-Hodgkin's lymphoma and for some cases of rheumatoid arthritis, targets and destroys CD20-positive B cells. In several small studies, the overall response rate to I.V. rituximab given at a dosage of 375 mg/m² weekly for 4 consecutive weeks was slightly more than 50%, with 25% to 30% of patients achieving complete responses. The response rates, which were variable and based on a combined analysis, did not differ significantly between splenectomized and nonsplenectomized patients. Responses occurred both early in the course of infusions and after discontinuation. Adverse effects were mostly first-infusion reactions of grade 1 or 2 severity.

Cines and Bussel discussed the use of rituximab (375 mg/m² intravenously weekly for 4 weeks) in patients in whom splenectomy had failed. The researchers reported that responses usually occurred within 4 to 8 weeks after the initial infusion, but some took place up to 4 months later. They reported a complete or partial remission rate of 25% to 50%; many remissions were durable. Adverse effects such as fever, chills, and hypotension were mostly related to first infusion. Apart from the reactivation of hepatitis B virus in chronic carriers, serious infection was rare despite the profound and prolonged peripheral B-cell suppression in all patients.

**Platelet Transfusion**

Platelet transfusion is one of several urgent measures used to stem serious episodes of internal and mucocutaneous bleeding in patients with ITP. Platelet transfusion is one of several urgent measures used to stem serious episodes of internal and mucocutaneous bleeding in patients with ITP. Platelet transfusions have been shown to increase platelet levels by at least 20,000/mcL in 42% of cases and have also been shown to be effective in controlling bleeding irrespective of increases in the platelet count. Side effects of the transfusions can include: fevers, infection and in severe cases, sepsis.

**Other Treatments Used in Chronic And Refractory ITP**

No single treatment algorithm is effective for all patients with chronic or refractory ITP, so therapy must be individualized, with the goal of maintaining safe platelet counts and minimizing adverse effects; a platelet level of 30,000 to 50,000/mcL is typically considered appropriate in patients without additional risk factors. A low-dose course of corticosteroids is frequently tried as an initial strategy.

**Platelet transfusion is one of several urgent measures used to stem serious episodes of internal and mucocutaneous bleeding in patients with ITP.**

Other pharmacologic strategies that are sometimes employed involve the off-label use of agents that inhibit platelet removal, such as danazol, which has induced a favorable response in 20% to 40% of patients and sustained remission in some patients after 3 to 6 months of treatment. The response rate to treatment is low in patients with severe chronic refractory ITP. Adverse effects include headache, nausea, breast tenderness, maculopapular rash, weight gain, hair loss, myalgia, amenorrhea, and liver dysfunction.

The use of an immunosuppressive agent such as azathioprine is another therapy that is sometimes used for patients with a platelet count below 20,000/mcL who have failed to respond to other treatments, although it is not approved for use in ITP. Responses have been reported in 20% to 40% of patients treated for 2 to 6 months with azathioprine. Other immunosuppressants that have been used off-label in patients with chronic refractory ITP include cyclophosphamide and cyclosporine. Although not a direct treatment of ITP, another measure that is often considered is testing patients for *Helicobacter pylori* infection and treating those with positive results to eradicate the organism, which has been shown to be associated with the development of autoimmune diseases, including ITP.

**Pharmacist’s Role**

Pharmacists can play a key role in helping to ensure appropriate, safe, and effective use of medications in patients with adult ITP. The beneficial role of the pharmacist in the medication-use...
process has been well documented (although specific evidence for adult ITP is lacking)\textsuperscript{36-39} Leape and colleagues, for example, showed that pharmacist participation on physician rounds in the intensive care unit reduced by 66% the rate of preventable adverse drug events during ordering. The investigators also found that virtually all of the pharmacist’s recommendations relating to medication use (99%) were accepted by physicians.\textsuperscript{38} Additionally, the PHARM (Pharmacist in Heart Failure Assessment Recommendation and Monitoring) study\textsuperscript{39} found that the rate of mortality and heart failure events was significantly lower in a group of patients with heart failure treated by an interdisciplinary team that included a clinical pharmacist compared with a control group treated without the benefit of a pharmacist’s intervention.

For patients with adult ITP, pharmacist interventions can help to ensure safe medication therapy use at all points in the continuum of care. On admission, a pharmacist taking a medication history may be more thorough in determining (and alerting the physician to) a patient's use of prescription and over-the-counter medications—as well as alternative therapies—that increase bleeding risk (or conversely, increase the likelihood of a thromboembolic event). On the nursing units, pharmacists’ suggestions on physician rounds can often avoid preventable adverse drug events, as Leape showed. And at discharge, medication counseling by a pharmacist can increase patient adherence to prescribed therapies and help prevent medication errors that can lead to serious complications and readmission.

**Conclusion**

Treatment options for many patients with adult ITP are limited. Even if a therapy does succeed in raising the platelet count, it may prove intolerable over the long term because of severe side effects. The durability of the response also can be problematic, and the treatment choices are even fewer when chronic refractory ITP develops.

**References**


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**Self-test Answer Key**

1. True
2. True
3. False
4. False