Immune Thrombocytopenia
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Immune Thrombocytopenia

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Immune Thrombocytopenia

Thomas G. DeLoughery, MD, FACP

INTRODUCTION

Immune thrombocytopenia (ITP) is a common condition, affecting approximately 3.8 persons per 100,000 each year. However, much controversy exists about all aspects of the disease, with little “hard” data to base decisions on given the lack of randomized clinical trials to address most clinical questions. This manual reviews the presentation and diagnosis of ITP along with treatment options and also discusses the management of ITP in specific clinical situations.

PATHOGENESIS AND EPIDEMIOLOGY

ITP occurs due to autoantibodies binding to platelet surface proteins, most often to the platelet receptor glycoprotein IIb/IIIa (GPIIb/IIIa). These antibody-coated platelets then bind to Fc receptors in macrophages and are removed from circulation. The initiating event in ITP is unknown. It is speculated that the patient responds to a viral or bacterial infection by creating antibodies that cross-react with the platelet receptors. Continued exposure to platelets perpetuates the immune response. ITP that occurs in childhood appears to be an acute response to viral infection and usually resolves. ITP in adults may occur in any age-group but is seen especially in young women.

Although it had been thought that most adult patients who presented with ITP went on to have a chronic course, more recent studies have shown this is not the case. In modern series, the proportion of patients who are “cured” with steroids ranges from 30% to 50% of patients. In addition, it has been appreciated that even if patients have modest thrombocytopenia, no therapy is required as long as their platelet counts are over 30 x 10^3/μL. However, even using this cut-off, a considerable number of patients will require chronic therapy.

CLINICAL PRESENTATION AND DIAGNOSIS

Presentation can range from a symptomatic patient with low platelets found on a routine blood count to massive bleeding. Typically, patients first present with petechiae, small bruises 1 mm in size, on the shins. True petechiae are only seen in severe thrombocytopenia. Patients will also notice frequent bruising as well as bleeding from the gums. Patients with very low platelet counts will develop “wet purpura,” blood-filled bullae in the oral cavity. Life-threatening bleeding is a very unusual presenting sign unless other problems (trauma, ulcers) are present. The physical examination is only remarkable for stigmata of bleeding, such as the petechiae. The presence of splenomegaly or lymphadenopathy weighs strongly against a diagnosis of ITP. Many patients with ITP will note fatigue when their platelet counts are lower.

DIAGNOSIS

Extremely low platelet counts with a normal blood smear in an otherwise healthy patient is diagnostic of ITP. The platelet count cut-off for considering ITP is 100 x 10^3/μL as the majority of patients with counts in the 100 to 150 x 10^3/μL range will not develop more severe thrombocytopenia. Also, the platelet count decreases with age (9 x 10^3/μL per decade in 1 study), and this also needs to be factored into the evaluation. The finding of relatives with “ITP” should raise suspicion of congenital thrombocytopenia. One should question the patient carefully about drug exposure (see Drug-Induced Thrombocytopenia), especially about over-the-counter medicines, “natural” remedies, or recreational drugs.

There is no laboratory test that “rules-in” ITP; rather it is a diagnosis of exclusion. The blood smear should be carefully examined for evidence of microangiopathic hemolytic anemias (schistocytes), bone marrow disease (blasts, teardrop cells), or any other evidence of a primary bone marrow disease. In ITP, the platelets can be larger than normal, but finding some platelets the size of red cells should raise the issue of congenital thrombocytopenia. One should exclude pseudothrombocytopenia, which is the clumping of platelets due to a reaction to the EDTA anticoagulant in the tube. The diagnosis is established by drawing the blood in a citrated (blue top) tube to perform the platelet count.
There is no role for antiplatelet antibody assays given that these tests lack sensitivity and specificity. In a patient without a history of autoimmune disease or symptoms, empiric testing for autoimmune disease is not recommended.

Patients who present with ITP should be tested for both HIV infection and hepatitis C. These are the most common viral causes of secondary ITP, and both have prognostic and treatment implications. Some authorities would also recommend checking thyroid function, as hypothyroidism can present with thrombocytopenia or aggravate existing thrombocytopenia.

The role of bone marrow examination is controversial. Patients with a classic presentation of ITP (young woman, normal blood smear) do not require a bone marrow exam before therapy is initiated. Patients who do not respond to initial therapy should have a bone marrow aspiration. The rare entity amegakaryocytic thrombocytopenia can present with a clinical picture similar to ITP, but amegakaryocytic thrombocytopenia will not respond to steroids. Bone marrow aspiration reveals the absence of megakaryocytes in this entity. It is rare, however, that another hematologic disease is diagnosed in patients with a classic clinical presentation of ITP.

In the future, measurement of thrombopoietin and reticulated platelets may provide clues to diagnosis. Patients with ITP paradoxically have normal or only mildly elevated thrombopoietin levels. The finding of a significantly elevated thrombopoietin level should lead to questioning of the diagnosis. One can also measure “reticulated platelets,” which are analogous to the red cell reticulocytes. Patients with ITP (or any platelet destructive disorder) will have high levels of reticulated platelets. These tests are not recommended for routine testing but may be helpful in difficult cases.

### THERAPY

In general, therapy in ITP should be guided by the patient’s signs of bleeding and not by unquestioning adherence to measuring platelet counts, as patients tolerate their thrombocytopenia well. It is unusual to have life-threatening bleeding with platelet counts over $5 \times 10^9/\mu L$ in the absence of mechanical lesions. Despite the low platelets, the overall mortality associated with ITP is estimated to be only 0.3% to 1.3%. It is sobering that in one study the death rate from infections was twice as high as that from bleeding.

Rare patients will have antibodies that interfere with the function of the platelet, and these patients can have profound bleeding with only modestly lowered platelet counts. A suggested cut-off for treating newly diagnosed patients is a platelet count of $30 \times 10^9/\mu L$.

### INITIAL THERAPY

The primary therapy for ITP is glucocorticoids, either prednisone or dexamethasone. One choice is prednisone at a dose of 60 to 80 mg/day started at the time of diagnosis (Table 1). Most patients will respond by 1 week, although some patients may take up to 4 weeks to respond. When the platelet count is above $50 \times 10^9/\mu L$, the prednisone should be tapered over the course of several weeks. An alternative to prednisone is dexamethasone 40 mg/day for 4 days. This regimen may induce a more rapid rise in the platelet count, but it is unknown whether it holds any long-term advantage over prednisone. One advantage of dexamethasone is that patients only need to take medication for 4 days. Several single-arm studies have suggested high response and remission rates, but randomized trials comparing dexamethasone with prednisone are needed. In European studies, better responses were seen with multiple cycles of dexamethasone—6 cycles every 28 days (overall response of 89.2%, with 90% of responders having a sustained response for 15 months) or 4 cycles every 14 days (85.6% response rate, with 81% have a sustained response for 15 months).

For rapid induction of a response, there are 2 options. Intravenous immune globulin (IVIG) at 1 g/kg in a single dose or intravenous anti-D immune globulin (Rh[D] immune globulin intravenous) at 50 to 75 μg/kg in a single dose can induce a response in over 80% of patients in 24 to 48 hours. IVIG has

### Table 1. Acute Therapy of Immune Thrombocytopenia

<table>
<thead>
<tr>
<th>Therapy Type</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary therapy</strong></td>
<td>Prednisone $1 \text{mg/kg}$; when count is $50 \times 10^9/\mu L$, taper over the course of 4 weeks</td>
</tr>
<tr>
<td><strong>For bleeding patients or counts below $5\text{–}10 \times 10^9/\mu L$</strong></td>
<td>Immune globulin $1 \text{g/kg IV OR}$ Anti-D immunoglobulin $75 \text{μg/kg once}$</td>
</tr>
<tr>
<td><strong>Refractory patients</strong></td>
<td>Immune globulin $1 \text{g/kg IV PLUS}$ Anti-D $75 \text{μg/kg PLUS}$ Methylprednisolone $30 \text{mg/kg PLUS}$ Vincristine $1.4 \text{mg/m}^2$ (capped at 2 mg) OR Immune globulin $1 \text{g/kg continuous infusion over 24 hours and continuous infusion platelets (1 plateletpheresis unit/6 hours or 1 platelet concentrate/hour)}$</td>
</tr>
</tbody>
</table>
several drawbacks. One is that it may cause aseptic meningitis. Another is that the increased viscosity can induce ischemia in patients with vascular disease. Finally, there is a considerable fluid load delivered with the IVIG.

The use of anti-D is limited to Rh-positive patients who have not had a splenectomy. It should not be used in patients who are Coombs’ positive because of the possibility of provoking more hemolysis. Rarely, anti-D has been reported to cause a severe hemolytic disseminated intravascular coagulation (DIC) syndrome, which has led to restrictions in use. Although the drug can be rapidly given over 15 minutes, due to concerns about DIC current recommendations are to observe patients for 8 hours after their dose, with a check of the urine dipstick for blood at 2, 4, and 8 hours.

For patients who are severely thrombocytopenic and do not respond to initial therapy, there are 2 options for raising the platelet counts. One is to use combination therapy of IVIG, anti-D, methylprednisolone, and vincristine. The combination of IVIG and anti-D may be synergistic since they block different Fc receptors. A response of 71% has been reported for this combination therapy in a series of 35 patients. The other option is a continuous infusion of platelets (1 unit over 6 hours) and IVIG 1 g/kg for 24 hours. Response rates of 62.7% have been reported with this combination.

Patients with severe thrombocytopenia who relapse with reduction of prednisone or who do not respond to prednisone have several options for further management. Repeated doses of anti-D or IVIG can transiently raise the platelet count, and some patients may only need several courses of therapy over the course of many months. One study showed that 60% of patients could delay or defer therapy by receiving multiple doses of anti-D. However, 30% of patients did eventually receive splenectomy, and 20% of patients required ongoing therapy with anti-D. In a randomized trial comparing early use of anti-D to steroids to avoid splenectomy, there was no difference in splenectomy rate (38% versus 42%). Finally, an option, as previously mentioned, is to try a 6-month course of pulse dexamethasone 40 mg/day for 4 days, repeated every 28 days.

**TREATMENT OPTIONS FOR PATIENTS WHO DO NOT RESPOND TO INITIAL THERAPY**

For those patients who do not respond to initial ITP therapies, there are multiple options. These can be divided into several broad groups: curative therapies, thrombopoietin agonists, and anecdotal therapies.

**Curative Therapies**

**Splenectomy.** In patients with severe thrombocytopenia who do not respond or who relapse with lower doses of prednisone, splenectomy should be strongly considered. Splenectomy will induce a good response in 60% to 70% of patients and is durable in most patients. Recently, 2 large reviews of splenectomy have been published. In these reviews, the complete response (normal platelet count following splenectomy and for the duration of follow-up) rate was 67% and the total response (partial and complete response together) rate was 88% to 90%. Only 15% to 28% of patients have relapsed over 5 years, with most recurrences occurring in the first 2 years. Splenectomy carries a short-term surgical risk and the life-long risk of increased susceptibility to overwhelming sepsis, as discussed below. However, the absolute magnitude of these risks is low and is often lower than that of continued prednisone therapy or of continued cytotoxic therapy.

Timing of splenectomy depends on the patient’s presentation. Most patients should be given a 6-month trial of steroids or other therapies before proceeding to splenectomy. However, patients who persist with severe thrombocytopenia despite initial therapies or who are suffering intolerable side effects from therapy should be considered sooner for splenectomy. In the Kojouri et al review, multiple factors, such as responding to IVIG, were found not to be predictive of response to splenectomy.

The method of splenectomy appears not to matter. Rates of finding accessory spleens are just as high or higher with laparoscopic splenectomy and the patient can recover faster. In patients who are severely thrombocytopenic, open splenectomy can allow for quicker control of the vascular supply of the spleen.

Rates of splenectomy in recent years have decreased for many reasons. One is the acceptance of lower platelet counts in asymptomatic patients. Another is the availability of alternative therapies such as rituximab. Finally, despite abundant data for good outcomes, there is a concern that splenectomy responses are not durable. Although splenectomy will not cure every patient with ITP, splenectomy is the therapy with the most patients, the longest follow-up, and the most consistent rate of cure, and it should be discussed with every ITP patient who fails initial therapy and needs further treatment.

The risk of overwhelming sepsis varies by indication for splenectomy but appears to be about 1%. The use of pneumococcal vaccine and recognition of this syndrome have helped lessen the risk. Asplenic
patients need to be counseled about the risk of overwhelming infections and should be vaccinated for pneumococcus, meningococcus, and *Haemophilus influenzae*; they should also wear an ID bracelet.\textsuperscript{30-32} Patients previously vaccinated for pneumococcus should be revaccinated every 3 to 5 years. The role of prophylactic antibiotics is controversial for adults, but patients under the age of 18 years should be on penicillin VK 250 mg orally twice daily.

**Rituximab.** Rituximab has been shown to be very active in ITP. Most studies use the standard dose of 375 mg/m\(^2\) weekly for 4 weeks, but pilot studies have shown that a low-dose regimen of 100 mg weekly for 4 weeks may have the same response rate.\textsuperscript{33} The response time can vary, with patients either showing a rapid response or taking up to 8 weeks for their counts to rise. Although experience is limited, the response seems to be durable, especially in those patients whose counts rise over 150 x 10^\(^3\)/μL; in patients who relapse, a response can be re-induced with a repeat course.

Overall the response rate of rituximab is about 60%, but only approximately 20% of patients will remain in long-term remission.\textsuperscript{34} Patients can often go back into remission with further doses of rituximab. There is no evidence yet that “maintenance” therapy or monitoring CD19/CD20 cells can help increase the duration of remission.

Whether to give rituximab pre- or postsplenectomy is also uncertain. One advantage of the presplenectomy approach is that 20% of patients will be “cured” and in many the need for surgery can be delayed. Also, for patients with medical conditions that put them at high risk for complications with splenectomy, rituximab is a good option. However, it is unknown if there will be long-term consequences of rituximab as opposed to the well-defined long-term risks of splenectomy. There was an intriguing trial of patients who were randomized to dexamethasone alone versus dexamethasone plus rituximab upon presentation of ITP.\textsuperscript{35} The rituximab group had an overall higher rate of sustained remission at 6 months than the dexamethasone group—63% versus 36%. Interestingly, patients who failed their first course of rituximab but then were “salvaged” with rituximab/dexamethasone had a similar overall response rate of 56%, suggesting that saving the addition of rituximab for steroid failures may be an effective option. However, the durability of these responses has not yet been reported. Rituximab is the only curative option left for patients who have failed splenectomy, and this is where it has been used in practice most often.

Although not “chemotherapy,” rituximab is not without risks. Many patients can develop infusion reactions, which can be severe in 1% to 2% of patients. In a meta-analysis, the fatal reaction rate was 2.9%.\textsuperscript{34} Patients with chronic hepatitis B infection can have reactivation with initiation of rituximab therapy. Finally, the very rare but devastating complication of progressive multifocal leukoencephalopathy has been reported.

**Thrombopoietin Mimetics**

Studies starting with Dameshek and Miller have shown low platelet production in ITP.\textsuperscript{36} Despite the very low circulating platelet count, it has also been shown that levels of the platelet growth factor thrombopoietin are not raised.\textsuperscript{37} Seminal studies with recombinant thrombopoietin in the 1990s showed that ITP patients could respond to thrombopoietin, but formation of anti-thrombopoietin antibodies halted trials with the first generation of thrombopoietin. Recently, 2 thrombopoietin mimetics have been approved for use in patients with ITP.

**Romiplostim.** Romiplostim is a “peptibody,” a combination of a peptide that binds and stimulates the thrombopoietin receptor and an Fc domain to extend its half-life.\textsuperscript{38} It is administered in a weekly subcutaneous dose starting at 1 to 3 μg/kg. Use of romiplostim in ITP patients shows a response rate of 80% to 88%, with 87% of patients being able to wean off or decrease other anti-ITP medications.\textsuperscript{39} In a long-term extension study, the response was again high at 87%.\textsuperscript{40} These studies also showed a reduced incidence of bleeding.

The major side effect of romiplostim seen in clinical trials was marrow reticulin formation, which occurred in up to 5.6% of patients.\textsuperscript{39,40} The clinical course in these patients is the development of anemia and a myelophthisic blood smear with teardrop cells and nucleated red cells. These changes appear to reverse with cessation of the drug. Although the bone marrow shows an increase in reticulin formation, it rarely, if ever, shows the collagen deposition seen with primary myelofibrosis.

Thrombosis has also been observed in patients treated with romiplostim at a rate of 0.08 to 0.1 cases/100 patient-weeks,\textsuperscript{41} but it remains unclear if this is due to the drug, part of the natural history of ITP, or expected complications in older patients undergoing any type of medical therapy. Surprisingly, despite the low platelet counts, patients with ITP in one study showed double the risk of venous thrombosis, demonstrating ITP itself can be a risk factor for thrombosis.\textsuperscript{32} Long-term safety of any ITP agent is important, and these trials have shown no long-term concerns for other clinical problems such as liver disease.
**Eltrombopag.** The other available thrombopoietin agent is eltrombopag, an oral agent that stimulates the thrombopoietin receptor by binding the transmembrane domain and activating it. The drug is given orally starting at 50 mg/day (25 mg for patients of Asian ancestry or with liver disease) and can be dose escalated to 75 mg/day. The drug needs to be taken on an empty stomach. Eltrombopag also has been shown to be effective in treating chronic ITP, with response rates of 59% to 80% and reduction in use of rescue medications. As was observed with romiplostim, the incidence of bleeding was also decreased in the eltrombopag trials.

Eltrombopag shares with romiplostim the risk for marrow fibrosis. Its unique side effect is a 3% to 7% incidence of elevated liver function tests. These did appear to resolve in most patients, but liver function tests must be monitored in patients receiving eltrombopag. Eltrombopag is metabolized by CYP1A2 and CYP2C8, but the clinical relevance of this is unknown. If a patient being treated with eltrombopag is started on agents that affect CYP1A2 or CYP2C8, it would be prudent to follow that patient’s platelet count more closely.

**Clinical Use of Thrombopoietin Mimetics.** The clearest indication for use of thrombopoietin mimetics is in patients who have failed several therapies and remain symptomatic or are on intolerable doses of other medications such as prednisone. The clear benefits are their relative safety and high rates of success. The main drawback is the need for continuing therapy as the platelets will return to baseline shortly after these agents are stopped. Currently, there is no clear indication for one medication over the other. The advantages to romiplostim are great flexibility in dosing (1–10 μg/kg week) and no concerns about drug interaction. The drawback is the FDA requirement to administer the drug in a clinic rather than at home. Eltrombopag offers the advantage of oral use but has a limited dose range and potential for drug interactions. Both have been associated with marrow reticulin formation.

**Other Options**

Numerous options for treatment of ITP have been described in the literature, although most of these are anecdotal reports or studies that enrolled small numbers of patients and sometimes included patients with mild thrombocytopenia. However, these can be tried in patients who have failed standard therapies and have bleeding. The agents with the most data are danazol, vincristine, azathioprine, and cyclophosphamide.

Danazol 200 mg 4 times daily is thought to downregulate the macrophage Fc receptor. The onset of action may be delayed, and a therapeutic trial of up to 4 to 6 months is advised. Danazol is very effective in treating patients with antiphospholipid antibody syndrome who have ITP and may be more effective in premenopausal women. Once a response is seen, danazol should be continued for 6 months, and then an attempt at weaning the patient from the medication should be made. A partial response can be seen in 70% to 90% of patients, but a complete response is rare.

Vincristine 1.4 mg/m² weekly has a low response rate, but if a response is going to occur, it will occur rapidly within 2 weeks. Thus, a prolonged trial of vincristine is not needed; if no platelet rise is seen in several weeks, the drug should be stopped. Again, partial responses (50%–63%) are more common than complete response (0%–6%).

Azathioprine 150 mg orally daily, like danazol, demonstrates a delayed response and requires several months to assess for response. However, 19% to 25% of patients may have a complete response. Recently, it has been reported that the related agent mycophenolate 1000 mg twice daily is also effective in ITP.

Cyclophosphamide 1 g/m² intravenously repeated every 28 days has been reported to have a high response rate of up to 40%. Although considered more “aggressive,” this is a standard immunosuppressive dose and should be considered in patients with very low counts. Patients who have not responded to single-agent cyclophosphamide may respond to multi-agent chemotherapy with agents such as etoposide and vincristine plus cyclophosphamide.

**A PRACTICAL APPROACH TO THE REFRACTORY PATIENT**

One approach is to divide patients into “bleeders” and “nonbleeders.” Bleeders have either very low platelet counts (under 5 x 10^9/μL) or have had significant bleeding in the past. Nonbleeders have platelet counts above 5 x 10^9/μL and no history of severe bleeding. Bleeders who fail splenectomy should first start with rituximab since it is not cytotoxic and is the only other “curative” therapy (Table 2). Patients who fail rituximab should then be tried on thrombopoietin mimetics. Patients who fail these and still have severe disease with bleeding should receive aggressive therapy with immunosuppression. One approach to consider is bolus cyclophosphamide. If this is unsuccessful, then one can consider using a combination of azathioprine plus danazol. Since it may take 4 to 6 months for this combination to work, these patients...
may need frequent IVIG therapies to maintain a safe platelet count.

Nonbleeders should be tried on danazol and other relatively “safe” agents. If this fails, rituximab or thrombopoietin mimetics can be considered. Before one considers cytotoxic therapy, the risk of the therapy must be weighed against the risk of the thrombocytopenia. The mortality from ITP is fairly low (5%) and is restricted to patients with severe disease. Patients with only moderate thrombocytopenia and no bleeding are better served with conservative management. There is little justification for the use of continuous steroid therapy in this group of patients given the long-term risks of this therapy.

### SPECIAL SITUATIONS

#### SURGERY

Patients with ITP who need surgery either for splenectomy or for other reasons should have their platelet counts raised to a level above 20 to 30 x 10^3/μL before surgery. Most patients with ITP have increased platelet function and will not have excessive bleeding with these platelet counts. For patients with platelet counts below this level, an infusion of IVIG or anti-D may rapidly increase the platelet counts. If the surgery is elective, short-term use of thrombopoietin mimetics to raise the counts can also be considered.

#### PREGNANCY

Up to 10% of pregnant women will develop low platelet counts during their pregnancy. The most common etiology is “gestational thrombocytopenia,” an exaggeration of the lowered platelet count seen in pregnant women. Counts may fall as low as 50 x 10^3/μL at the time of delivery. No therapy is required as the fetus is not affected and the mother does not have an increased risk of bleeding. Pregnancy complications such as HELLP syndrome and thrombotic microangiopathies also present with low platelet counts, but these can be diagnosed by history.

Women with ITP can either develop the disease during pregnancy or have a worsening of the symptoms. Counts often dramatically drop during the first trimester. Early management should be conservative, with low doses of prednisone to keep the count above 10 x 10^3/μL. IVIG is also effective, but there are rare reports of pulmonary edema. Rarely, patients who are refractory will require splenectomy, which may be safely performed in the second trimester. For delivery the count should be greater than 30 x 10^3/μL, and for an epidural greater than 50 x 10^3/μL.

Most controversy centers on management of the delivery. In the past it was feared that fetal thrombocytopenia could lead to intracranial hemorrhage, and cesarean section was always recommended. It now appears that most cases of intracranial hemorrhage were due to alloimmune thrombocytopenia and not ITP. Furthermore, the nadir of the baby’s platelet count is not at birth but several days after. It appears the safest course is to proceed with a vaginal or cesarean-section delivery determined by obstetrical indications and followed immediately with checks of the baby’s platelet count. If the platelet count is low in the neonate, IVIG will raise the count. Since the neonatal thrombocytopenia is due to passive transfer of maternal antibody, the platelet destruction will abate in 4 to 6 weeks.

#### PEDIATRIC PATIENTS

The rate of ITP in children is 1.9 to 6.4 cases per 100,000 children per year. There are several distinct differences in pediatric ITP. Most cases will resolve in weeks, with only a minority of cases transforming into chronic ITP (5%–10%). The rates of serious bleeding are lower, with rates of intracranial hemorrhage of 0.1% to 0.5% being seen. For most patients without bleeding or with mild bleeding, management is expectant due to the perception that the risks of therapies are more concerning than the risks of bleeding. For patients with bleeding, IVIG, anti-D, or a short course of steroids can be used. Given the risk of overwhelming sepsis, splenectomy is often deferred as long as possible. There is growing use of rituximab due to concerns over use of agents such as cyclophosphamide or azathioprine in children. Studies of the use of thrombopoietin mimetics in the pediatric population are starting to appear.

### HELICOBACTER PYLORI

There has been much interest in the relationship between *H. pylori* and ITP. *H. pylori* infec-

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**Table 2. Therapeutic Options in Patients Not Cured with Splenectomy**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose/Regimen</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rituximab</td>
<td>375 mg/m² weekly for 4 weeks</td>
</tr>
<tr>
<td>Thrombopoietin mimetics</td>
<td></td>
</tr>
<tr>
<td>Azathioprine</td>
<td>125 mg/day</td>
</tr>
<tr>
<td>Cyclophosphamide</td>
<td>1 g/m² repeated every 28 days</td>
</tr>
<tr>
<td>Danazol</td>
<td>200 mg 4 times daily ± azathioprine</td>
</tr>
<tr>
<td>Mycophenolate</td>
<td>1000 mg twice daily</td>
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Immune Thrombocytopenia

I m m u n e  T h r o m b o c y t o p e n i a

T able 3. Common Critical Care Drugs Implicated in Thrombocytopenia

<table>
<thead>
<tr>
<th>Antimicrobial</th>
<th>Amphotericin B</th>
<th>Linezolid</th>
<th>Piperacillin</th>
<th>Rifampin</th>
<th>Trimethoprim-sulfamethoxazole</th>
<th>Vancomycin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antiseizure</td>
<td>Carbamazepine</td>
<td>Phenytoin</td>
<td>Valproic acid</td>
<td></td>
<td></td>
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<tr>
<td>H₂-blockers</td>
<td>Cimetidine</td>
<td>Ranitidine</td>
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<td></td>
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<td></td>
</tr>
<tr>
<td>Nonsteroidal anti-inflammatory agents</td>
<td>Ibuprofen</td>
<td>Naproxen</td>
<td>Acetaminophen</td>
<td>Amiodarone</td>
<td>Anti-GPⅡb/Ⅲa agents</td>
<td></td>
</tr>
<tr>
<td>Gold</td>
<td>Haloperidol</td>
<td>Heparin</td>
<td>Oxaliplatin</td>
<td>Quinidine</td>
<td>Quinine</td>
<td></td>
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<tr>
<td>Statin lipid-lowering agents</td>
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</tbody>
</table>


DRUG-INDUCED THROMBOCYTOPENIA

Patients with drug-induced thrombocytopenia present with very low (<10 x10⁹/μL) platelet counts 1 to 3 weeks after starting a new medication.⁶⁰–⁶² In patients with a possible drug-induced thrombocytopenia, the primary therapy is to stop the suspected drug.⁶³ If there are multiple new medications, the best approach is to stop any drug that has been strongly associated with thrombocytopenia (Table 3). IVIG, corticosteroids, or intravenous anti-D have been suggested as being useful in drug-related thrombocytopenia. However, since most of these thrombocytopenic patients recover when the agent is cleared from the body, this therapy is probably not necessary and holding it avoids exposing the patients to the adverse events associated with further therapy.

EVANS SYNDROME

Evans syndrome is defined as the combination of autoimmune hemolytic anemia (AIHA) and ITP.⁶⁴,⁶⁵ These cytopenias can present simultaneously or sequentially. Patients with Evans syndrome are thought to have a more severe disease process, to be more prone to bleeding, and to be more difficult to treat, but the rarity of this syndrome makes these features hard to quantify.

The classic clinical presentation of Evans syndrome is severe anemia and thrombocytopenia. Children with Evans syndrome often have complex immunodeficiencies such as autoimmune lymphoproliferative syndrome.⁶⁶ In adults, Evans syndrome most often complicates other autoimmune diseases such as lupus. There are increasing reports of Evans syndrome occurring as a complication of T-cell lymphomas. Often the autoimmune disease can predate the lymphoma diagnosis by months or even years.

In theory the diagnostic approach is straightforward by showing a Coombs'-positive hemolytic anemia in the setting of a clinical diagnosis of ITP. The blood smear will show spherocytes and a diminished platelet count. The presence of other abnormal red cell forms should raise the issue of an alternative diagnosis. It is uncertain how vigorously one should search for other underlying diseases. Many patients will already have the diagnosis of an underlying autoimmune disease. The presence of lymphadenopathy should raise the concern for lymphoma.

Initial therapy is high-dose steroids (2 mg/kg/day). IVIG should be added if severe thrombocytopenia is present. Patients who cannot be weaned off prednisone or who relapse after prednisone should be considered for splenectomy, although these patients are at higher risk of relapsing.⁶⁴ Increasingly, rituximab is being...
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used with success. For patients who fail splenectomy and rituximab, aggressive immunosuppression should be considered. A reasonable choice would be bolus cyclophosphamide 1 g/m². For patients with Evans syndrome due to underlying lymphoma, anti-neoplastic therapy often results in prompt resolution of the symptoms. Recurrence of the autoimmune cytopenias often herald relapse.

CONCLUSION

Over the past decade, there have been substantial changes in both our understanding of ITP and the therapy available for treating it. Many adults who develop ITP may have only self-limited disease and may not require therapy. Primary therapy is glucocorticoids, and new agents such as rituximab and the thrombopoietin mimetics are now available. However, there is still a need for more clinical trials to better define therapy for this common hematologic disease.

BOARD REVIEW QUESTIONS

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REFERENCES

75 microg/kg/d of i.v. anti-D increases the platelet count more rapidly and for a longer period of time than 50 microg/kg/d in adults with immune thrombocytopenic purpura. Brit J Haem 2001;112:1076–78.


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