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Perspective

CME Article

Splenectomy for immune thrombocytopenia: down but not out

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Splenectomy is an effective therapy for steroid-refractory or dependent immune thrombocytopenia (ITP). With the advent of medical alternatives such as rituximab and thrombopoietin receptor antagonists, the use of splenectomy has declined and is generally reserved for patients that fail multiple medical therapies. Splenectomy removes the primary site of platelet clearance and autoantibody production and offers the highest rate of durable response (50% to 70%) compared with other ITP therapies. However, there are no reliable predictors of splenectomy response, and long-term risks of infection and cardiovascular complications must be considered. Because the long-term efficacy of different second-line medical therapies for ITP have not been directly compared, treatment decisions must be made without supportive evidence. Splenectomy continues to be a reasonable treatment option for many patients, including those with an active lifestyle who desire freedom from medication and monitoring, and patients with fulminant ITP that does not respond well to medical therapy. We try to avoid splenectomy within the first 12 months after ITP diagnosis for most patients to allow for spontaneous or therapy-induced remissions, particularly in older patients who have increased surgical morbidity and lower rates of response, and in young children. Treatment decisions must be individualized based on patients' comorbidities, lifestyles, and preferences. Future research should focus on comparing long-term outcomes of patients treated with different second-line therapies and on developing personalized medicine approaches to identify subsets of patients most likely to respond to splenectomy or other therapeutic approaches. (*Blood*. 2018;131(11):1172-1182)

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Disclosures

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Learning objectives

Upon completion of this activity, participants will be able to:

1. Describe the efficacy of splenectomy and predictors of treatment response in patients with immune thrombocytopenia (ITP), based on a review.
2. Determine the safety of splenectomy in patients with ITP.
3. Discuss overall recommendations for use of splenectomy in patients with ITP.

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Introduction

Immune thrombocytopenia (ITP) is characterized by immune-mediated destruction of circulating platelets and suppression of platelet production.[1] ITP occurs either as a primary disorder or secondary to underlying neoplasia, infection, or autoimmune disease; in the latter case, there may be more profound immune dysregulation.[2]

The spleen plays a critical role in the pathogenesis of ITP (Figure 1). For most patients, the spleen is the primary site of platelet clearance. Splenic macrophages expressing FcγR mediate the uptake of antibody-coated platelets[3,4] with phagocytosis mediated through SYK signaling pathways.[5] The spleen also serves as a critical niche for immune cells that promote anti-platelet antibody formation.[6] Splenic macrophages present antigenic peptides derived from platelet glycoproteins (primarily GPIIa/IIIb or GPIb/IX) to $CD4^+$ T cells, causing activation and expansion of autoreactive B and T cells.[7,8] $CD4^+$ T cells express CD40 ligand (CD40L) that engages CD40 on B lymphocytes to drive their differentiation into plasma cells and promote autoantibody production.[9] The spleen also serves as a reservoir for long-lived, anti-platelet antibody-producing plasma cells.[10-12] Even in the current era, when effective medical therapies for ITP are available, splenectomy is associated with a higher rate of long-term remission than any other ITP therapy,[13-15] presumably reflecting removal of the site of platelet clearance and autoantibody production.

For decades, splenectomy was the standard of care for steroid-refractory ITP patients. With the availability of rituximab and the thrombopoietin receptor agonists (TPO-RAs), the decision to perform splenectomy is now frequently delayed until late in the disease course. In a recent study spanning 1980 to 2015, 18.7% of ITP patients ultimately underwent splenectomy, although splenectomy was most commonly used as third-line therapy.[16]

Efficacy of splenectomy for ITP

In ~80% of patients with ITP, platelet counts increase immediately postsplenectomy, and 50% to 70% of patients achieve durable remission.[13-15,17] A retrospective multicenter study of 402 patients reported a response rate of 86% (66% complete response, 20% partial response); 75% of responses were maintained after a median follow-up of 92 months.[18] In a systematic review of case series published between 1966 and 2004, 1731 (66%) of 2623 adults maintained a complete response after a median follow-up of 29 months.[13] In another systematic review, 72% of patients maintained a response at 5 years.[19] Similar response rates have been observed when splenectomy was used as a second- or third-line treatment.[20] However, many patients in these older studies underwent splenectomy soon after failing corticosteroids and/or intravenous immunoglobulin (IVIg). Response rates are likely to be lower in more contemporary studies, in which splenectomy candidates were more likely to have failed rituximab and TPO-RA. Likewise, elderly patients may not demonstrate the same robust response to splenectomy as younger individuals.[21] There is no role for partial or subtotal splenectomy in ITP, although splenic irradiation has been used with some success.[22]

Postsplenectomy relapses occur in 20% to 30% of patients, often within the first 24 months.[23] Patients who relapse after splenectomy may respond to subsequent medical therapies, and stable platelet counts can be achieved in most individuals[23]; however, a subset of patients who are refractory to medical therapies experience high morbidity and mortality.[24]

Both the 2011 American Society of Hematology (ASH) guidelines[25] and the International Working Group Consensus report[26] recommend splenectomy as a second-line therapy for ITP. Although the International Working Group guidelines do not state a preference between splenectomy, rituximab, or TPO-RA, ASH guidelines give splenectomy a higher recommendation. Although the use of rituximab or TPO-RAs may delay or obviate the need for splenectomy over the short term, long-term outcomes of patients undergoing splenectomy or receiving medical treatment have not been compared. Thus, there remains uncertainty as to the optimal sequence of ITP therapy.

Predictors of response to splenectomy

The success of splenectomy is difficult to predict, and statistics on response rates apply to populations rather than individuals. Predictors of splenectomy response that have been evaluated follow below.

Clinical predictors

Studies examining patient and disease characteristics that predict response to splenectomy have yielded inconsistent results. In a systematic review of 135 case series, younger age was most consistently associated with response (median ages 32-51 years vs 40-73 years for responders and nonresponders, respectively).[13,27] This review did not establish an age cutoff, and splenectomy responses were still observed in older adults (age >65 years). However, other studies reported higher relapse rates in elderly patients, with long-term responses achieved in only 50%.[21,28] Moreover, comorbidities often present in elderly patients contribute to increased perioperative complications.[29]

Other clinical factors that have been examined include the duration of ITP and the presence of underlying disorders such as systemic

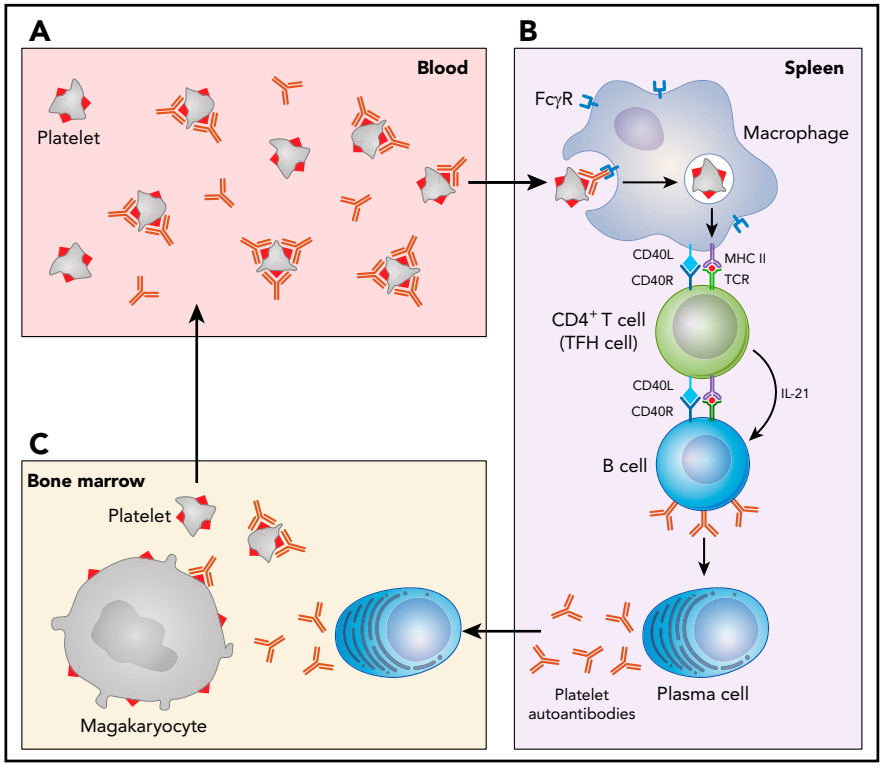

Figure 1. The spleen in the pathogenesis of ITP. (A) Autoantibodies bind to antigens on platelets, primarily gpIIb/IIIa, and gpIb/IX. (B) Splenic macrophages expressing FcγR internalize antibody-coated platelets, degrade them, and present platelet glycoprotein-derived peptides to autoreactive $CD4^+$ T cells, which on activation interact with B cells through the CD40/CD40L interaction leading to somatic hypermutation and class switching. Autoreactive B cells differentiate into antiplatelet antibody-producing plasma cells that either stay in the spleen or migrate to the blood and bone marrow. (C) Megakaryocytes in the bone marrow express platelet glycoproteins such as gpIIb/IIIa and gpIb/IX, and autoantibodies against these antigens impair platelet production and contribute to megakaryocyte apoptosis. Circulating CD8 positive can also cause thrombocytopenia by direct cytotoxicity (not shown).

lupus erythematosus (SLE), common variable immunodeficiency (CVID), hepatitis C, and antiphospholipid antibodies (APLAs); however, their effects have been inconsistent across studies.[13] A high platelet count within the first week after splenectomy has been reported to predict long-term response.[30,31]

Prior therapies

Response to corticosteroids and IVIg has been correlated with response to splenectomy in univariate analyses, but not in multivariable models.[31] In 1 study (n = 30), response to IVIg was highly correlated with response to splenectomy[32]; however, in another study, 6/7 patients who failed corticosteroids and IVIg responded to splenectomy.[33] A small retrospective series of 14 adults reported that a response to the last dose of anti-D was predictive of response to splenectomy, although there was no overall correlation between anti-D use and splenectomy responses.[34] Taken together, we believe that previous responses to these therapies help to confirm the diagnosis of ITP,[35] thus making a response to splenectomy somewhat more likely in these patients compared with patients who do not respond.

Platelet scintigraphy

Indium-labeled autologous platelet scanning, in which ^{111}In-labeled autologous platelets are infused into the patient and subsequent scintigraphy reveals the site of platelet clearance,[36] emerged as a promising predictor of splenectomy response in the 1980s but has not been widely adopted. In a pooled analysis of 6 case series (n = 580), splenectomy responses were observed in 91.4% (range 87.0% to 94.8%) of patients with a splenic pattern and 40.9% (range 15.4% to 100%) of patients with a hepatic, diffuse, or mixed pattern.[37-43] However, these studies used different scintigraphic techniques and response criteria, and length of follow-up varied. Indium-labeled autologous platelet scanning is technically challenging and not widely available[44]; thus, it cannot be universally recommended. More studies are needed to evaluate its predictive value across centers.

Safety of splenectomy

Complications associated with splenectomy can be divided into perioperative/short-term and long-term risks.

Perioperative and short-term risks

Laparoscopic splenectomy has replaced open splenectomy as the technique of choice because of decreased postoperative pain, shorter hospitalization, faster recovery, and decreased cost.[13] In a systematic review of more than 3000 splenectomies for ITP, laparoscopic splenectomy had lower mortality (0.2% vs 1.0%) and complication rates (9.6% vs 12.9%) than open splenectomy.[13] The relatively high rate of complications despite advances in surgical techniques and anesthesia may be, in part, because of the increased recognition of ITP in older adults and the higher surgical risk in these patients.[45] Superior outcomes with laparoscopic splenectomy have been observed by more experienced surgeons in high-volume centers.

Postoperative bleeding is the most common cause of death in patients who undergo splenectomy.[45] Adequate hemostasis is usually achieved with platelet counts $\geq 20 \times 10^9$/L to 30×10^9/L; and corticosteroids, IVIg, or other therapies may be used to raise platelet counts before surgery.[46] Some series demonstrate that splenectomy can be performed safely even in patients with very low platelet counts,[47] although others report more complications.[48]

The risk of overwhelming infection by encapsulated bacteria is the most concerning side effect of splenectomy. This risk is highest in the few months immediately following splenectomy.[49] Presplenectomy vaccinations against *Streptococcus pneumoniae*,

Table 1. Recommended strategies to prevent early and late complications after splenectomy

Complication	Early	Late
Surgical morbidity	Careful patient selection: older patients and those with comorbidities are less attractive candidates for surgery and anesthesia. Alternative therapies should be considered.	
Bleeding	Laparoscopic splenectomy Elevation of platelets to $>30 \times 10^9$/L to 50×10^9/L using steroids, IVIg (or TPO-RA if no response to these)	
Infection	Vaccination against *S pneumoniae*, *H influenzae* type b, and *N meningitidis*, ideally at least 2 wk prior to surgery Education about the risk of postsplenectomy sepsis. Emphasize need for early administration of antibiotics in case of fever. Consider prophylactic antibiotics postoperatively.	Repeat vaccination against *S pneumoniae* every 5 y, annual influenza vaccine Patients may be at higher risk of babesiosis and malaria and should be aware of this if traveling to endemic areas.
Vascular complications Early Postoperative VTE including acute portal/splenic vein thrombosis Late VTE Atherothrombotic events	Early mobilization, hydration, and initiation of prophylactic anticoagulation once hemostasis has been ensured in patients with other risk factors for thrombosis	Address modifiable risk factors (smoking, obesity, etc.). Aspirin may be prescribed for patients with cardiovascular risk factors. Thromboprophylaxis in the setting of elective surgery or other situations that increase thrombotic risk

Hemophilus influenzae type b, and *Neisseria meningitidis* have dramatically reduced the incidence of postsplenectomy sepsis.[50] It is most efficient to routinely vaccinate adult patients before splenectomy even if they had received these as routine childhood vaccinations; otherwise, antibody titers may be checked, and repeat vaccines can be administered as needed. Vianelli et al reported no cases of fatal sepsis after 402 splenectomies with a median follow-up of 57 months.[18]

Antibiotic prophylaxis with amoxicillin (or erythromycin) is recommended for children postsplenectomy. The practice of postsplenectomy antibiotic prophylaxis in adults is empiric and differs among the authors, ranging from no prophylaxis to 3 to 6 months postoperatively. A longer duration of antibiotic prophylaxis should be considered for high-risk patients, including children <5 years of age, patients with a poor response to vaccination, and immunocompromised patients. Patients should be educated about the risk of serious infection and should seek immediate medical attention and receive anti-pneumococcal antibiotics at the first sign of infection. The meningococcal serogroup B vaccine (Bexsero) can be considered in addition to the conjugate vaccine in younger patients (<25 years).

Perioperative thromboembolism, particularly portal-splenic vein thrombosis (PSVT) is a recognized complication of splenectomy. In a population-based study of 9976 patients with ITP of which 1762 underwent splenectomy, the rate of PSVT in splenectomized vs nonsplenectomized patients was 1.6% vs 1%, and the rate of other venous thromboembolism (VTE) was 4.3% vs 1.7%.[51] In contrast, in a Danish cohort of 3812 patients who underwent splenectomy, only 0.39% developed PSVT.[52] There are no standard recommendations regarding perioperative thromboprophylaxis for splenectomy, but it should be considered in patients at high risk because of comorbidities or prior thrombosis.

Long-term risks

Few studies on long-term outcomes after splenectomy separately consider patients who undergo splenectomy specifically for ITP, and even fewer compare these to an ITP cohort not undergoing splenectomy.

Infection The risk of overwhelming bacterial sepsis in asplenic patients is well recognized.[53] With presplenectomy vaccination, this risk has been reduced from ~7.16 per 100 person-years[50] to 2.3 per 100 patient-years.[54] A more recent analysis from the Danish National Patient Registry that compared patients who underwent splenectomy with the general population, patients undergoing appendectomy, and disease-matched controls who did not undergo splenectomy reported an 18-fold higher infection rate during the first 90 days postoperatively in patients undergoing splenectomy compared with the general population; this risk decreased to 4.6-fold at 91 to 365 days after splenectomy and 2.5-fold at >365 days after splenectomy.[55] For ITP patients undergoing splenectomy compared with those who did not, the absolute rate of infection was 5.6% vs 2.7% in the first 90 days, 5.7/100 patient-years vs 6.5/100 patient-years from day 91 to 365, and 4.6/100 patient-years vs 3.3/100 patient-years after day 365. In both studies, enteric organisms rather than encapsulated bacteria were the main cause of early and late postsplenectomy sepsis. Moreover, beyond 90 days, ITP patients who had undergone splenectomy had lower mortality than ITP patients who had not.[49] Indeed, the infection risk associated with chronic corticosteroid or other immunosuppressive therapy in patients with chronic ITP may exceed that of appropriately vaccinated patients who undergo splenectomy.[56] Long-term measures to mitigate postsplenectomy infections are similar to those used perioperatively (Table 1).

Although less frequently than splenectomy, rituximab is also a risk factor for infections in patients with ITP with a reported hazard ratio

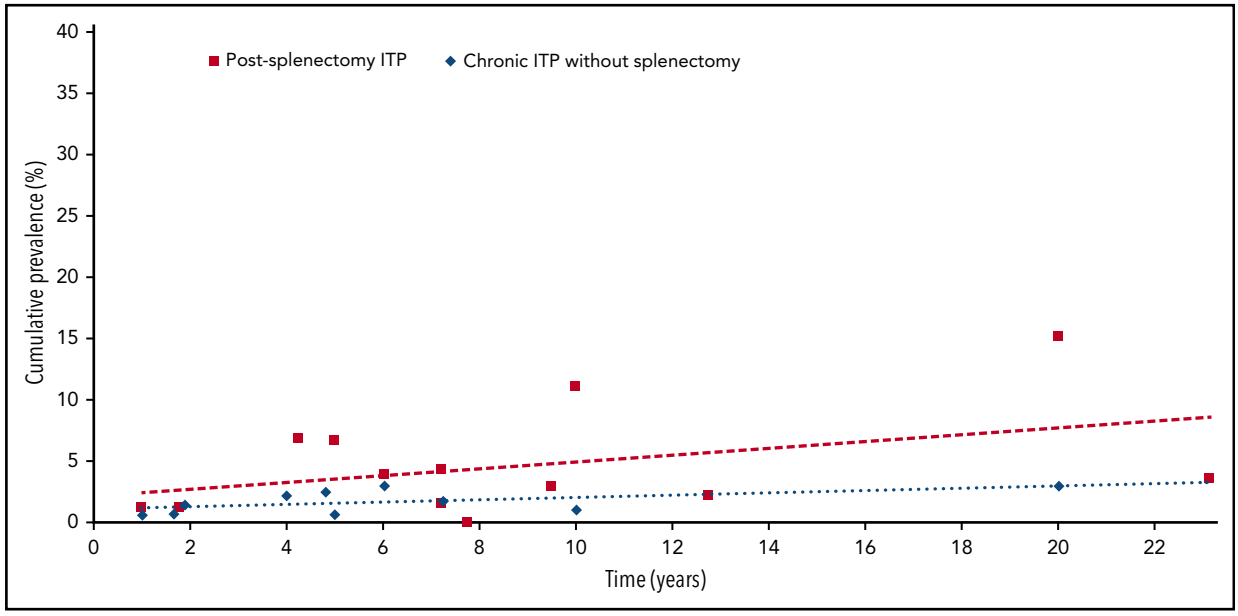

Figure 2. Cumulative prevalence of venous thromboembolic events in ITP patients who underwent splenectomy compared with those who did not. There is an increased rate of VTE in patients with ITP that underwent splenectomy vs those who did not; however, the absolute risk is low in both groups. We included population-based/administrative cohort studies (N = 5) and retrospective (N = 7) and prospective (N = 2) cohort studies that reported outcomes on at least 50 patients with ITP, with a median follow-up >3 months.[22,55,68-72] For the splenectomy patients in particular, we included only studies that reported late (>3 months) VTE events to minimize selection bias from studies focusing on postoperative portal and splenic vein thrombosis. Time is calculated from date of splenectomy in the splenectomy group and date of enrollment in cohort for the nonsplenectomy group. When only median follow-up was provided, means were approximated as described by Wan et al.[73] Some selection bias is possible because the patients that underwent splenectomy may have had more severe disease than the comparison group.

(HR) of 2.60 (95% confidence interval [CI], 1.67-4.03).[57,58] Reactivation of hepatitis B infection following rituximab therapy is well appreciated,[59] and patients with latent infection should receive antiviral therapy during and for 6 months after completing treatment. Rituximab has also been associated with rare cases of progressive multifocal leukoencephalopathy because of John Cunningham virus; these generally occurred in patients that had also received other immunosuppressive therapies for long durations.[60] Rituximab can attenuate the response to vaccination[61] for 6 to 12 months after treatment, a consideration that may be particularly important for patients who subsequently undergo splenectomy. Therefore, we recommend administering pre-splenectomy vaccines before treatment with rituximab.

Cardiovascular complications The strongest evidence for a procoagulant state following splenectomy applies to patients who undergo this procedure for hemolytic anemia.[62] The mechanisms underlying the association between splenectomy and cardiovascular events are not well understood. Surgery per se increases the short-term VTE risk, and this may be compounded by elevated platelet counts and hematocrit,[63] persistence of procoagulant damaged erythrocytes, erythrocyte and platelet-derived microparticles,[64] and altered lipid profiles following splenectomy.[65] In patients with ITP, splenectomy usually increases the platelet count and may also result in increases in plasma cholesterol, leukocyte counts, and C reactive protein, all of which are associated with increased thrombotic risk.

VTE The rate of VTE among patients with ITP (4.05 to 5.32 per 1000 patient-years) is increased compared with the general population,[66,67] and splenectomy may further increase this risk. In a Danish cohort, the risk of VTE in the first year after splenectomy for any indication was 1.9% compared with 0.3% for the general population.[52] Compared with the general population, the risk of VTE was lower for those who underwent splenectomy for ITP than for the entire splenectomized cohort (odds ratio = 2.7 [95% CI, 1.1-6.3] vs odds ratio = 3.2 [95% CI, 2.4-4.2]). Other studies that followed patients for at least 1 year after splenectomy for ITP have reported a cumulative prevalence of VTE ranging from 1.4% to 16%, depending on length of follow-up.[18,51,68-72] A prospective cohort study of ITP patients who underwent splenectomy reported the highest rates of VTE, 11% at 10 years, 15% at 20 years, and 21% at 30 years,[71] which may be because of the prospective study design with closer follow-up. However, the cohort was small and significant attrition resulted in few patients followed beyond 20 years.

Few studies have directly compared ITP patients who did or did not undergo splenectomy. In a retrospective study, the hazard ratio for VTE >90 days after splenectomy was 2.7 (95% CI, 1.9-38).[51] A multicenter cohort study also noted that splenectomy increased VTE risk (HR = 4.1 [95% CI, 1.1-15.7]).[67] The highest incidence of VTE is in the perioperative period and during the first year after splenectomy, but an increase in the cumulative incidence of VTE has been noted for up to several decades. Compiling data from studies with extended follow-up, the risk of thrombosis among splenectomy patients was higher than that for patients with ITP who did not undergo splenectomy (Figure 2).[73]

Arterial thromboembolism (ATE) An early study of veterans who underwent splenectomy for trauma reported a twofold increased risk of death from ischemic heart disease.[74] Subsequent reports confirmed higher rates of stroke and myocardial infarction in adults with hereditary spherocytosis who underwent splenectomy, with an incidence of 22% to 32% by age 70.[75] The

Table 2. Splenectomy vs TPO-RA and rituximab in refractory/relapsed ITP

Therapy	Response rate and durability	Time to response	Adverse effects	Contraindications	Preferred in	Approximate cost
Splenectomy	Overall response rate >80%, 50%-75% at 5 y	Days	Surgical mortality (<0.2% with laparoscopic splenectomy), surgery-related complications (9.6%; bleeding, infection, thrombosis) Lifetime risk of overwhelming sepsis Possible vascular complications: VTE, ATE	Multiple comorbidities, poor surgical candidate Relative: advanced age (higher rate of complications, lower response rate at age >60-70) *Helicobacter pylori*, hepatitis C (treat underlying cause first)	Fulminant ITP refractory to corticosteroids/IVIg with poor response to TPO-RA, desire to avoid drug therapy or close medical monitoring, uncertain compliance with medical therapy, prohibitive cost of medical therapy	20 000 USD
TPO-RA (eltrombopag and romiplostim)	80% overall response rate, high rates of durable response on continued therapy	10-14 d	Headache, rebound thrombocytopenia, elevated liver enzymes (eltrombopag), bone marrow reticulin fibrosis, possible small increased risk of venous thrombosis	Pregnancy (category C) and lactation, MDS Caution in patients with liver disease and a history of thrombosis	Patient preference, patients not interested in or unable to undergo splenectomy	Annually ~108 000 USD*
Rituximab	60% overall response rate; 21%-26% of responders at 1 y have responses at 5 y	1-8 wk	Infusion-related adverse events (fever, chills, dyspnea, hypotension), neutropenia, hypogammaglobulinemia, reactivation of viral infections (hepatitis B), progressive multifocal leucoencephalopathy (rare)	Active hepatitis B infection, pregnancy (category C) and lactation	Patient preference, patients not interested in or unable to undergo splenectomy, patient seeks medical long-term remission	10 000-40 000 USD per 4-infusion course

MDS, myelodysplastic syndrome; USD, United States dollars.

*Cost is estimated based on average wholesale cost for the following doses: eltrombopag 50 mg daily and romiplostim 3 μg/kg per week for a 70-kg individual.

rate of ATE is 3.2% to 4.5% in patients with chronic ITP,[67,76] and Ruggeri et al reported that splenectomy increased this risk (HR = 3.2 [95% CI, 1.2-8.6]).[67] However, in a recent population-based study, the rates of myocardial infarction (1.13% vs 1.30%) and stroke (2.09% vs 2.56%) were similar for ITP patients who did or did not undergo splenectomy.[77] Thus, although splenectomy may increase the risk of ATE overall, the effect in ITP patients is unclear.[71,77]

Pulmonary arterial hypertension is a reported complication in patients who have undergone splenectomy, particularly for sickle-cell disease, thalassemia intermedia, stomatocytosis, and spherocytosis, all hemolytic disorders.[62] This complication is likely related to the underlying red cell disorder, perhaps contributing to a hypercoagulable state, rather than the splenectomy per se.[77,78] Studies have not identified an elevated risk for pulmonary artery hypertension in ITP patients postsplenectomy.[79,80]

Other second-line approaches to ITP therapy

There is a lack of randomized trials comparing different second-line therapies for ITP; rituximab, TPO-RA, and splenectomy all warrant consideration in patients who relapse after initial corticosteroid therapy or are corticosteroid dependent. Table 2 provides a comparison of these agents. Response rates to agents such as azathioprine, mycophenolate, cyclosporine A, cyclophosphamide, and others, particularly when used as single agents, are sufficiently low that these drugs are relegated to the third line or higher setting.[81]

Rituximab

In a systematic review that included 313 ITP patients who received rituximab at a dose of 375 mg/m^2 for 4 weeks, responses were observed in 62.5% of patients with median time to response of 5.5 weeks and a median duration of 10.5 months.[57] Rituximab is commonly used in ITP because of the potential for long-term remission; 1 study reported that 21% and 26% of adults and children, respectively, with complete responses at 1 year maintained these responses at 5 years, respectively.[82] Another study found that combination therapy with dexamethasone and rituximab in patients with ITP of >2 years duration yielded long-term response rates similar to those expected with splenectomy, particularly in females.[83] However, a randomized study that enrolled corticosteroid-resistant ITP patients with a median ITP duration of 37 weeks failed to demonstrate a higher rate of long-term responses with rituximab.[84] Thus, whether rituximab is able to induce long-term remissions of ITP, or whether studies suggesting that it may do so reflect the natural history of the disease, remains unresolved. Rituximab can delay the need for splenectomy,[85] and many would advocate a trial of rituximab before splenectomy or TPO-RA because of the potential for long-term response.

TPO-RA

TPO-RAs are approved for treatment of ITP in children and adults. As with rituximab, the place of TPO-RA in the sequence of ITP therapy is not established. TPO-RAs have class-specific toxicities, in particular bone marrow reticulin fibrosis in 2% to 4% of patients.[86] Eltrombopag is associated with elevated transaminase levels, which in rare patients may progress to hepatotoxicity.[87] Response to either eltrombopag or romiplostim occurs in 80%, and the development of resistance is uncommon.[86,88] Although it was not expected that these agents should induce remission, a recent report suggests that ~30% of early stage ITP patients are able to discontinue these agents and maintain stable platelet counts.[89,90] Similar to rituximab, some of these remissions may reflect the natural history of ITP.

Safety of splenectomy in special situations

Pregnancy

Primary approaches to ITP in pregnancy involve corticosteroids and/or IVIg.[91] Other agents, such as azathioprine and cyclosporine, have been used safely; however, even when effective, these may take considerable time to raise the platelet count. Rituximab is not teratogenic but may cause prolonged B-cell lymphopenia in offspring.[91] Splenectomy is rarely used in pregnant patients with ITP; when it is, the optimal time is in the mid–second trimester to minimize the risk of premature labor and provide access to the spleen before it is obscured by the gravid uterus.

Children

Over 75% of children with ITP recover spontaneously, and because serious bleeding is rare, patients are often managed expectantly.[92,93] ITP refractory to steroids and/or IVIg is uncommon and should prompt consideration of a congenital thrombocytopenia.[92] Splenectomy is effective in children with ITP with responses seen in 80%[82,92,93] and is justified in children with persistent severe thrombocytopenia refractory to other treatments. However, because of uncertainty as to the time course and role of the spleen in development of the immune repertoire, as well as reports suggesting that in some cases childhood ITP may remit years after initial onset,[93] splenectomy is deferred as long as possible and reserved for patients with refractory disease and bleeding. Prophylactic penicillin is recommended until the age of 5 in young children or for at least 2 years after splenectomy in older children.[94,95]

Primary alternatives to splenectomy in children include rituximab and TPO-RA. Rituximab has similar efficacy in children as in adults, with initial and 5-year response rates in children of 57% and 26%, respectively.[82] Appropriate vaccination should be confirmed prior to use of rituximab. Eltrombopag and romiplostim, both approved for treatment of ITP in children, are effective and may also be used to delay or defer splenectomy.[96-98] There is relatively little experience with long-term use of TPO-RA in children.

CVID

CVID is associated with autoimmune cytopenias, most frequently ITP. Although splenectomy has been employed for management of ITP in these patients, the possibility that splenectomy may worsen an existing immunodeficiency is concerning. The European Society of Immunodeficiencies described 48 patients with CVID who underwent splenectomy. Thirty-six patients had autoimmune cytopenias, and 8 of the 11 patients with ITP who underwent splenectomy responded.[99] Nine patients developed overwhelming postsplenectomy infection with encapsulated organisms (infection rate 2.47 per 100 patient-years), 6 of whom had not been receiving immunoglobulin. Seven of the 9 episodes occurred within 3 years of splenectomy. Ten patients died, 4 from unusual infections, although 2 of the 4 had been on long-term immunosuppression.[99]

Splenectomy was not associated with mortality in another cohort of 473 patients with CVID, of which 39 underwent splenectomy with only a single infectious episode in a patient not receiving immunoglobulin.[99] These reports suggest that splenectomy is relatively safe in patients with CVID, despite a small increase in infection risk that may be reduced by immunoglobulin replacement. Similarly, splenectomy appears to be safe and effective in patients with HIV and ITP.[100,101]

SLE and APLAs

Autoimmune thrombocytopenia occurs in 8% to 10% of patients with SLE, and splenectomy appears to be equally effective (65% to 85% responses) in this population compared with patients with primary ITP, without an increase in morbidity.[102] APLA occur in up to 40% of patients with ITP.[103] Although these antibodies do not alter the course of ITP, several studies suggest that the presence of APLA, particularly the lupus anticoagulant, increases the risk of thrombosis,[103,104] with 5-year thrombosis-free survival of 39.9% and 97.7%, respectively, in patients with ITP and lupus anticoagulant, vs ITP alone. A small study reported no significant increase in thrombotic events after splenectomy in patients with ITP and APLA, although there was a trend toward more arterial events.[105] Although there is insufficient data available to discourage splenectomy in patients with APLA, aggressive thromboprophylaxis in the perioperative period should be employed.

Lymphoproliferative disorders

ITP is a well-recognized complication of lymphoproliferative disorders such as chronic lymphocytic leukemia (CLL), non-Hodgkin lymphoma, and Hodgkin disease and is frequently autoantibody mediated, although there is no evidence that the malignant clone is the source of the autoantibodies.[106] These disorders are also associated with impaired B-cell differentiation and skewing of B-cell subsets, and ITP associated with lymphoproliferative disorders is often less responsive to first-line treatment with corticosteroids.[2] For example, in a cohort of 1278 patients with newly diagnosed CLL of which 64 developed ITP, steroids and/or IVIg had a response rate (complete response and partial response) of only 48.4% (16 of 33 patients).[107] The addition of CLL-directed cytotoxic therapy improved response rate (16 of 22; 72.7%).[107] Splenectomy appears to be safe in individuals with lymphoproliferative disorders,[108] although these individuals are often older with comorbidities, and surgical risks must be considered. Splenectomy has been reported to be effective in some cases of CLL-associated ITP[109-111]; however, as with other causes of secondary ITP, treatments directed at the underlying disorder should be attempted before splenectomy.

Perspective: deciding on splenectomy

The decision to proceed with splenectomy in a specific patient depends on the characteristics of their ITP as well as their age, general health, lifestyle, and goals. Because there are few data comparing long-term outcomes of splenectomy with other second-line approaches, it is difficult to provide evidence-based recommendations, and patient preferences weigh heavily in treatment decisions.[112] If possible, we defer splenectomy for 12 months after ITP onset to allow for a possible spontaneous or therapy-induced remission to occur. Before splenectomy or even second-line medical therapies, it is important to rule out underlying conditions that may contribute to persistent or recurrent thrombocytopenia. The differential diagnosis of thrombocytopenia is wide and includes disorders such as hypersplenism, chronic infection, inherited and drug-mediated thrombocytopenias, bone marrow failure, and pseudothrombocytopenia. Moreover, causes of secondary ITP such as HIV or hepatitis C infection, *Helicobacter pylori* infection in endemic regions, and lymphoproliferative and autoimmune disorders should be considered, because in these cases treatment of the underlying disorder may be a more efficient and effective means of improving the platelet count. Bone marrow examination is not necessary in all patients but should be considered in older patients, particularly in the presence of other cytopenias, and in patients with poor responses to first-line ITP therapies.

There are several situations in which we would strongly consider splenectomy. Occasionally, patients present with severe ITP characterized by profound thrombocytopenia, bleeding, a poor or transient response to corticosteroids and IVIg, and a suboptimal response to TPO-RA. Because the onset of the therapeutic effect or rituximab may take weeks to months in ITP, we would not recommend its use in such patients. Instead, splenectomy provides an expeditious and generally effective approach. Even if splenectomy does not result in a complete remission, the response to subsequent interventions with previously used agents may improve.

Young patients with an active lifestyle, including those who participate in contact sports or high-risk activities, may prefer splenectomy. These individuals may wish to avoid frequent office visits and platelet count monitoring, as well as the imposition of chronic medical therapy. For these patients, the long-term risk of infection after splenectomy may be minimized through vaccination, patient education, and rapid institution of antibiotic therapy at the earliest indication of infection. They should also be counseled on the risk of thrombosis.

Other patients who may benefit from splenectomy include those who are noncompliant with medications or for whom medical alternatives are inaccessible.

There are also patients for whom we would discourage splenectomy, including those in their first year since diagnosis and those with multiple comorbidities that worsen surgical risk. Finally, because the long-term success rate of splenectomy may be lower,[21] and the surgical risk higher in elderly patients, a trial of medical therapy may be preferred in these individuals.

Conclusions

The development of new medical therapies for ITP has at the same time broadened but complicated treatment approaches for patients and providers. Presently, the choice of different second-line treatment options, including splenectomy, must be made with minimal data concerning long-term outcomes. Although the use of splenectomy has declined substantially with the development of new medical therapies, it remains the most cost-effective second-line treatment of ITP. At the same time, splenectomy is associated with surgical complications, infection, and thrombotic risks that might tip the balance in favor of medical treatment of many patients. Future research directions in ITP should focus on comparative long-term outcomes of patients treated with different second-line therapies, expanded splenectomy response data for patients who fail rituximab and/or TPO-RA, and development of personalized medicine

approaches to identify subsets of patients most likely to respond to splenectomy or other second-line therapies.

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Footnote

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