CHEST

Critical Illness in Patients With Asplenia

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The critically ill, asplenic patient presents a variety of management challenges. Historically, the focus of the care of the asplenic population has been the prevention and management of infection, including the often-fatal overwhelming postsplenectomy infection with encapsulated organisms such as *Streptococcus pneumoniae*. Recently, however, there has been increasing recognition of the spleen's function in areas outside of immunity because the asplenic state has been identified as a risk factor for such vascular complications as thrombosis and pulmonary hypertension resulting from dysregulated inflammation and coagulation. Because of the relatively small size of this population and the relative infrequency with which critical illness occurs in it, there are few controlled trials that can serve as a basis for therapeutic maneuvers; thus, optimal management requires an astute clinician with an understanding of the pathogenetic mechanisms underlying the reported consequences of splenectomy. The purpose of this review is to explore the pathophysiology of the asplenic state—impairment in adaptive immunity, loss of blood filtration, endothelial dysfunction, and dysregulated coagulation—and how it leads to infection, thrombosis, and pulmonary hypertension as well as to discuss the implications of these conditions on the management of the critically ill, splenectomized patient.

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Critical care management of the patient who was postsplenectomy has focused on the risk factors, prevention, and outcomes associated with overwhelming postsplenectomy infection (OPSI). This emphasis without consideration of the pathophysiologic abnormalities and noninfectious complications associated with the postsplenectomy state predisposes the clinician to cognitive bias from availability (jumping to a diagnosis that comes to mind quickly because it is common, serious, recently encountered, or otherwise noteworthy) or anchoring (staying locked on to a diagnosis made early on despite disconfirming evidence).[1]

Three major categories of the indications for splenectomy exist: traumatic, neoplastic, and hematologic.[2] Increasing awareness of the importance of the spleen in the immune response has led to increasing efforts into preservation of the spleen in victims of trauma.[3,4] As a result, patients who are postsplenectomy are now less common and more likely to have concomitant hematologic or immunologic conditions.[5] Few systematic investigations of critical illness in the asplenic population exist, with the highest quality of evidence often being single-center case series. Because of the lack

ABBREVIATIONS: CR1 = complement receptor 1; IVIG = IV immunoglobulin; OPSI = overwhelming postsplenectomy infection; PH = pulmonary hypertension; RV = right ventricular

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of systematic evidence in this population, the purpose of this review is to highlight for the intensivist the significant pathophysiologic concepts and potential management considerations in the critically ill, asplenic population.

OPSI, with a mortality of nearly 50%,[6] is the most feared complication of splenectomy. It is, however, important to note that OPSI is but one complication of asplenia. Subsequent data have reinforced that clinicians must both recognize the increased risk of overwhelming sepsis in patients who are postsplenectomy and understand the consequences of splenectomy on the cardiovascular system, including atherothrombosis, venothromboembolism, and pulmonary vascular disease.

Pathophysiology and Clinical Implications of Splenectomy

The long-term infectious complications of splenectomy have been well-described in the medical literature.[7] On a conceptual basis, clinicians can consider the spleen an organ involved in phagocytosis and destruction of pathogens and abnormal or damaged red blood cells, induction of adaptive immune responses, and modulation of inflammation.

Infection

The spleen's red pulp filters blood and removes senescent erythrocytes, and the loss of this phagocytic function in asplenic patients creates three clinically important considerations in critical illness. Because of its role in facilitating the phagocytosis of infected erythrocytes, the spleen's red pulp plays a role in the defense against intraerythrocytic parasitic infections such as babesiosis and malaria; loss of phagocytosis leads to ongoing infection, hemolysis, increased severity of illness, and mortality in asplenic patients.[8,9] Much more common are infections in asplenic patients by encapsulated bacteria (with *Streptococcus pneumoniae* being the classic pathogen), in part from the loss of splenic removal of circulating, unopsonized bacteria. For this reason, the organism number in the blood of asplenic patients may be high enough to allow detection on buffy coat staining. Finally, the spleen, along with the liver, removes C3b-opsonized immune complexes bound to complement receptor 1 (CR1) without lysis or sequestration of the erythrocytes.[10]

The spleen's white pulp, with its T- and B-cell compartments, participates in adaptive immunity and antibody production. Although the liver, bone marrow, and peripheral lymph nodes can assume many of these essential immunologic functions after splenectomy, the spleen provides the largest population of marginal zone B cells. These B cells initiate the humoral immune response, which is important in the defense against encapsulated organisms.[11,12] For example, the lack of circulating B1-a B cells—a type of pneumococcus memory B cells—is considered an important reason that asplenic patients suffer from a lack of intravascular pathogen filtering and specific antibody production.[13]

Another important function of the spleen is modulation of the inflammatory cascade. Swirski et al[14] found that the murine spleen is a major reservoir of noncirculating, undifferentiated monocytes. These monocytes, released in times of stress, migrate to target tissues, differentiate into macrophages, and perform a variety of functions in addition to fighting infection, including promoting healing and tissue repair.[15] Splenectomy removes an important reservoir of these diversely functional cells. The spleen is also a specific and essential target of the cholinergic antiinflammatory pathway, which inhibits proinflammatory cytokine production by vagal nerve-mediated signaling through the α7 nicotinic acetylcholine receptor subunit. Splenectomized mice who received nicotine, an α7 agonist that mimics vagus nerve stimulation, had an increase in proinflammatory cytokine production and lethality from polymicrobial sepsis, indicating that the spleen is essential to the α7nACdhR-dependent protective antiinflammatory response. Conversely, in nonsplenectomized mice, administration of nicotine protects mice against the lethality of polymicrobial sepsis by inhibiting proinflammatory cytokine production via an α7 nicotinic acetylcholine receptor. The depletion of splenic nicotinic acetylcholine receptors following splenectomy contributes to increased levels of tumor necrosis factor and the marked inflammatory response.[16] The spleen, therefore, lies at an important crossroads between innate and adaptive immunity, and its loss can lead to impairment of phagocytic functions, dysfunction in both adaptive and innate immunity, and up-regulation of the inflammatory cascade.

Thrombosis

Though the spleen has long been recognized as playing a crucial role in the conveyance of immunity, less recognized is its role in the pathophysiology of vascular disease, pulmonary hypertension (PH), and VTE. The cardiovascular and septic complications of splenectomy may be seen as the result of a common

pathway of hypercoagulability, platelet activation, and inflammation[17,18]; the spleen may function to regulate each of these processes.

The tong-term risk for venous and arterial vascular complications of patients having undergone splenectomy increases in the setting of hematologic disease. In a survey of 8,860 patients with beta-thalassemia in the Mediterranean and Middle East, Taher et al[19] found the prevalence of thrombotic events to be 1.65%. Strikingly, 94% of these events occurred in asplenic patients, and similar associations have been observed in patients with other hemolytic processes. Crary and Buchanan[20] reported an increased risk of VTE in splenectomized patients with hemolytic processes other than beta-thalassemia. Two other series demonstrated an increase in stroke, myocardial infarction, and coronary or carotid artery surgery in splenectomized patients with hereditary spherocytosis (5.6-fold increased rate; hazard ratio, 7.2).[21,22]

The risk of these vascular complications appears to be associated with ongoing intravascular hemolysis, thrombocytosis, nucleated RBCs, and transfusion naivety.[20,23] The mechanism may result from chronic inflammation and endothelial dysfunction. Erythrocyte membrane abnormalities, circulating microparticles, and cell-free hemoglobin from hemolysis have been shown to alter the vascular endothelium by interfering with nitric oxide metabolism and function.[24] These changes promote vasoconstriction, smooth muscle proliferation, and endothelial and platelet activation, especially in pulmonary circulation.[20,25]

Alterations in the phospholipid composition of the erythrocyte cell membrane provide a procoagulant surface for increased thrombin formation and hypercoagulability in thalassemia.[26,27] Furthermore, patients with thalassemia have altered endothelial adhesion molecules that may further contribute to hemostasis and vascular occlusion; following splenectomy, these patients have elevated P-selectin levels, indicating ongoing platelet activation.[28,29] These changes may compound when combined with the postsplenectomy leukocytosis, thrombocytosis, and increased hemoglobin, cholesterol, and C-reactive protein levels. Interestingly, the presence of significant erythrocytic abnormalities such as waste material "pits" on the peripheral smear may identify asplenic patients at a higher risk for sepsis.[30,31] Although the pathophysiologic mechanisms associated with this observation require further study, the current understanding suggests that microcirculatory dysfunction resulting from both diminished erythrocyte deformability and impaired oxygen and CO_2 exchange may contribute to the finding.

Given the pathogenic similarities between hematologic dysregulation in patients having undergone splenectomy for hemolytic anemia and with sepsis (including endothelial dysfunction and the dysregulation of coagulation), one can postulate parallels between the fulminant course of sepsis (in its most extreme form, purpura fulminans[32]) and the chronic predisposition to macrovascular and microvascular thrombosis in the asplenic patient. Research now implicates the platelet as a major prothrombotic and pro-inflammatory contributor in sepsis pathogenesis. Additionally, investigators postulate that platelet dysfunction is a cause of both hypercoagulability and thrombotic events associated with splenectomy, especially in the small pulmonary arteries. Atichartakarn et al[33] found that patients with hemoglobin E/beta-thalassemia and splenectomy had hyperactive platelets (defined as hyperaggregation in response to adenosine diphosphate, thrombin, and ristocetin) when compared with normal control subjects and patients with hemoglobin E/beta-thalassemia and without splenectomy. There was also an increased level of plasma thrombin, indicating that these patients had ongoing intravascular coagulation.

PH

Splenectomy is a risk factor for PH through complex mechanisms, including the aforementioned phenomena of inflammation and thrombosis.[20] The reported incidence of PH in splenectomy patients is 8% to 11.5%.[34,35] Furthermore, the prevalence of PH in asplenic patients with hemoglobinopathies such as thalassemia and sickle cell disease may be even higher, with reported rates consistently exceeding 30%.[36-38] Many observational studies also note an association between splenectomy and chronic thromboembolic PH.[39] Because of the multifactorial nature of these mechanisms, the most recent guidelines moved PH associated with splenectomy and chronic hemolytic anemia to World Health Organization Group 5 (PH with unclear, multifactorial mechanisms).[40]

Robinette and Fraumeni[41] published an important case series in 1977 describing a long-term increase in the risk of death in 740 World War II servicemen who underwent splenectomy for trauma. In addition to pneumonia, the authors also noted an increased risk of death resulting from heart disease. Earlier reports of

increased deaths from ischemic heart disease following splenectomy have been called into question,[41] as recent studies only describe this increase in patients with hereditary spherocytosis.[20] Interestingly, Newman et al[42] reported that many subjects in a large cohort of patients with familial pulmonary arterial hypertension were misdiagnosed with other cardiovascular conditions, including "heart attack." This raises the possibility that prior cardiac deaths may have been misclassified because of the technological limitations of the time.

These data suggest that the intensivist should be vigilant for both infectious and vascular complications after splenectomy: thrombosis/VTE, PH, and possibly cardiovascular disease. Shock in the critically ill, postsplenectomy patient may be due to the vasodilatory effect of overwhelming sepsis, left ventricular dysfunction from preexisting coronary artery disease, or right-heart failure resulting from preexisting PH or acute thromboembolic disease. A systematic strategy considering all of these conditions is important in choosing the appropriate strategy of resuscitation and hemodynamic support.

Management Considerations

Advances in the care of patients who had undergone splenectomy have led to reduced rates of infection and mortality, due in large part to vaccination,[43] education, and early antibiotic administration.[44] Despite these efforts, the mortality of postsplenectomy patients who are infected with *S. pneumoniae* and *Haemophilus influenzae* type B still approaches 50%.[6] Successful treatment of the critically ill, asplenic patient requires incorporation of the pathophysiologic considerations discussed previously into a proactive treatment plan including early, appropriate antibiotic therapy, effective resuscitation, and the awareness of thrombotic risk to minimize the risk of end-organ dysfunction.

Treatment of Infection

Because of the importance of achieving early, appropriate antibiotic therapy in the treatment of infection, the clinician must have an understanding of the pathogens for which asplenic patients are at increased risk. An approach to the pathogens causing sepsis in asplenic patients is summarized in Table 1.[7,45] Initially proposed in 1986, the categories of classic, clearly implicated, and possibly involved pathogens continue to have practical application in understanding both pathogenesis and treatment.[45]

TABLE 1] Pathogens Causing Increased Severity of Infection in Patients With Asplenia

Classic	Clearly Implicated[a]	Possibly Involved
Streptococcus pneumoniae	*Haemophilus influenzae* type b *Capnocytophaga canimorsus* *Capnocytophaga cynodegmi* *Babesia microti* *Plasmodium* species *Bordetella holmesii*	*Neisseria meningitidis* *Escherichia coli* *Staphylococcus aureus*

[a]Based on pathogenetic mechanisms.
Data from Scully et al,[45] Rubin and Schaffner,[7] and Bach et al.[9]

S. pneumoniae is by far the most common etiologic agent associated with OPSI, causing at least 80% of infections according to a 16-year literature review.[46] In Table 1, it is referred to as the classic pathogen in asplenic patients. An increasingly recognized pathogen since its identification in 1983, *Bordetella holmesii* is now included among the pathogens for which splenectomy is an important risk factor.[47] A population-based study in Denmark of postsplenectomy bacteremia or meningitis found enteric pathogens (most commonly, *Escherichia coli*) and *Staphylococcus aureus* were most common.[48] The authors reported only one case resulting from *S. pneumoniae* in this series.

The role of the spleen in defense against malaria is not understood. There have been occasional and contradictory reports about the susceptibility of splenectomized individuals to *Plasmodium falciparum*.[9] The review by Rubin and Schaffner noted that it has not been definitively established that malaria is more severe in asplenic people than in those with an intact spleen.[7] In contrast, a prospective controlled study of 33 splenectomized Malawian adults found that a partially immune population of asplenic individuals was at increased risk of malarial infections and illness, with significantly higher parasite densities and more mature parasitic forms in peripheral blood.[9] In the context of these data, malaria has been listed in Table 1 in the category of clearly implicated pathogens.

Properdin deficiency has been described in association with fulminant meningococcal disease.[49] Even though work in the early 1980s suggested the spleen was essential for propagation of the alternate complement pathway by certain substances such as properdin in response to infection,[50] subsequent work identified the endothelium as a physiological source of properdin.[51,52]

Because the spleen is not the primary source of properdin, meningococcal infection is classified in Table 1 as being possibly involved with asplenia. Despite this, treatment and vaccine recommendations target meningococcus in asplenic patients, with a similar strategy recommended for the clearly implicated pathogen *H. influenzae*.

Despite the severity and mortality of sepsis in patients following splenectomy, there are no prospective clinical trials defining optimal therapy. Cefepime and vancomycin have been recommended for adult asplenic patients who appear acutely ill.[7] An alternate empiric regimen includes vancomycin plus either ceftriaxone, levofloxacin, or ciprofloxacin.[53] These regimens provide coverage against *S. pneumoniae*, *S. aureus*, *H. influenzae*, *Neisseria meningitidis*, and sensitive Enterobacteriaceae. If concern for resistant gram-negative pathogens exists, these choices should be modified to include directed coverage for these organisms. A cephalosporin should be favored over fluoroquinolone therapy in the setting of proven or suspected central nervous system infection.

The combination of an attenuated host inflammatory response and the inflammatory nature of *S. pneumoniae* raises important considerations. The inflammatory response to pneumococci is one of the most potent in medicine,[54] and macrolides have been shown to induce an immunomodulatory effect that attenuates the production of inflammatory cytokines.[55] Patients hospitalized with community-acquired pneumonia have been shown to exhibit lower pulmonary and systemic inflammatory cytokine profiles and stabilize more quickly after at least 72 h of antibiotic therapy including a macrolide.[56] In a prospective, multicenter cohort study of patients with severe sepsis and septic shock from severe community-acquired pneumonia, macrolide use was associated with lower ICU mortality compared with fluoroquinolones (hazard ratio, 0.44; 95% CI 0.20-0.95; $P = .03$).[57] A systematic review and meta-analysis of the role of macrolides on mortality in critically ill patients with community-acquired pneumonia[58] suggested that the mortality differences might be related to the nonantimicrobial immune modulatory properties of macrolides. A study in critically ill patients with ventilator-associated pneumonia[59] demonstrated that treatment with clarithromycin restored the balance between pro- and anti-inflammatory mediators in patients with sepsis. Although not specifically studied in the splenectomy population, the pleiotropic anti-inflammatory effect of a macrolide in combination with a β-lactam antibiotic might prove beneficial in the empiric therapy of critically ill asplenic patients.

The role of IV immunoglobulin (IVIG) in the management of infections in patients with defective humoral immunity has not been definitively established. A Cochrane analysis did not recommend the routine use of IVIG as adjunctive therapy in patients with bacterial sepsis or septic shock, because, although mortality was reduced among some adult patients with sepsis, this benefit was not seen in trials with a low risk of bias.[60] Although the authors noted that polyclonal IVIG reduced mortality among some adult patients with sepsis, this benefit was not seen in trials with low risk of bias. The conclusion was that adjunctive therapy with monoclonal IVIG remains experimental.

Despite the absence of data examining IVIG in the management of OPSI, potential benefits include limitation of complement activity, neutralization of harmful toxins, and anti-inflammatory immunomodulation. Specific antibody supplemented with IVIG has been shown to play a crucial role in OPSI in a mouse model, adding to prior research suggesting that IVIG can improve OPSI survival by increasing phagocytosis by specific antibody in the liver.[61] These data provide a theoretical basis for IVIG in the management of OPSI until clinical trials in asplenic patients with sepsis are available.

Clinical Implications of the Increased Risk of Thrombosis

Kaplan et al[62] recently reported that the presence of severe sepsis and septic shock is associated with a high incidence (37.2%; 95% CI, 28.3-46.8) of VTE despite appropriate prophylaxis. Though the etiology of these findings is unclear, the prothrombotic, inflammatory state of severe sepsis and septic shock is the suspected cause. Given the similarities between the inflammatory milieu of sepsis and the inflammatory dysregulation imparted by asplenia, in addition to the increased risk of VTE seen in both populations, the risk may be even higher in the septic, asplenic patient than in the patient with either condition alone. The treating clinicians should have heightened awareness for VTE in these patients, even in the setting of appropriate prophylactic measures.

Resuscitation and Hemodynamic Management with Possible Right Ventricular Dysfunction

Several recent trials have systematically examined elements of the landmark study that used an early

TABLE 2] Issues of Importance in the Stepdown from Critical Care Units

	Contextual Comment	Recommendations
Antibiotics at home	To be taken at first sign of infection if healthcare system cannot be accessed within 2 h; then seek immediate medical care[7]	• Amoxicillin/clavulanate or cefuroxime or fluoroquinolone[53] • Amoxicillin or levofloxacin or moxifloxacin[7]
Prophylactic antibiotics	Variability of recommendations in adults[44]	• No specific US guideline or recommendation • Consideration on lifelong basis for asplenic person who has survived an episode of postsplenectomy sepsis[7] • British guideline noting that life-long prophylaxis might be offered to continued high-risk asplenic patients (but grade B and C levels of evidence)[72]
Immunization	In addition to usual immunization recommendations in adults, including influenza A, special comment about what is termed "risk-specific recommended vaccines" (ie, pneumococcal, Meningococcal, and *Haemophilus influenzae* type b)[73]	• *Streptococcus pneumoniae* immunization with both 13-valent conjugate vaccine and 23-valent polysaccharide vaccine o 8-wk interval between doses if conjugate vaccine given first o 1-y interval between doses if polysaccharide vaccine given first • *H. influenzae* type b: single dose (if not administered in infancy) • *Neisseria meningitidis*: booster every 5 y after the initial dose
Education	Despite evidence that improved understanding of their condition may prevent postsplenectomy complications in the asplenic patient population,[74] many of these patients remain poorly educated on their condition[75]	• Inform patients and caregivers of increased risk of certain infections • Encourage communication with their primary care physician as well as specialists, dentists, etc. • Consider medical alert bracelet • Reiterate the importance of all of these modalities

goal-directed therapy protocol and the subsequent Surviving Sepsis Guidelines that followed it for the management of severe sepsis and septic shock.[63] The Protocolized Care for Early Septic Shock (ProCESS),[64] Australasian Resuscitation in Sepsis Evaluation (ARISE),[65] and Protocolised Management in Sepsis (ProMISe)[66] trials demonstrated that usual care without rigid requirements for central venous access, central venous oxygen saturation monitoring, and aggressive transfusion strategies resulted in similar outcomes when compared with early goal-directed therapy. Early goal-directed therapy patients received more fluid, blood, dobutamine, and invasive procedures with a greater cost of care.[64-66]

Intrinsic cardiac dysfunction is present in up to 40% of all patients with sepsis, and reductions in the ejection fraction and stroke work index of the left and right ventricles has been associated with a poor prognosis in patients with an intact spleen.[67] The etiology of this observed myocardial depression is multifactorial and includes reductions in myocardial blood flow and contractility resulting from direct effects from endotoxin and the host inflammatory response, microcirculatory dysfunction, alterations in intracellular calcium trafficking, and dysregulation of nitric oxide synthesis.[68]

Because splenectomy is a risk factor for both VTE and PH, the intensivist should consider splenectomized patients to be at risk for both acute and chronic right ventricular (RV) dysfunction. The presence of underlying significant PH only compounds this pathophysiologic process, leading to further reductions in RV stroke volume, progressive dilation, and worsening left ventricular filling through the principle of interventricular dependence.[69] In many cases of RV dysfunction and/or failure, the clinician will be alerted to elevated RV filling pressures by using physical examination (elevated jugular venous pressures), invasive hemodynamic monitoring (elevated central venous pressure), or echocardiography. As such, asplenic patients who exhibit elevated RV filling pressures without significant improvement in cardiac output during resuscitation should be considered to have RV dysfunction. RV function is further challenged by acute increases in afterload associated with sepsis-induced

ARDS and mechanical ventilation. There is a growing trend toward noninvasive evaluation of intravascular volume status using inferior vena cava measurements. It is important to recognize that splenic vein clamping can decrease portal vein flow by 30%, which may result in subsequent inferior vena cava changes following splenectomy and confound the interpretation of these data.[70] When RV dysfunction is suspected, ECG, echocardiography, or, in some cases, right-heart catheterization may be required to confirm its presence.[69]

Once the clinician makes the diagnosis of RV dysfunction, the management can be challenging. Reversible causes such as pulmonary embolism and RV infarction should be ruled out and, if present, managed appropriately. Volume management of RV dysfunction is critical, as, in many cases, further volume resuscitation and rising central venous pressure can have a detrimental effect on cardiac output; indeed, the appropriate management may be to reduce RV volume by diuresis to improve hemodynamics.[71]

Prevention of Further Illness

Once a patient recovers from splenectomy-associated critical illness and the treatment team feels that step-down is appropriate, the intensivist should take appropriate steps to communicate with the patient, family members and the accepting service four important aspects in the long-term management of this patient population: (1) patient-administered oral antibiotics at the onset of fever; (2) prophylactic antibiotics; (3) immunization; and (4) patient/family education. These are summarized in Table 2.

Summary

The spleen is an important component in the modulation of immunity, thrombosis, and inflammation. In the asplenic patient, these alterations can result in systemic consequences of purpura fulminans or widespread microvascular dysfunction as well as localized vascular processes of thrombosis, myocardial infarction, or PH. What is unclear is which asplenic patients will develop these fulminant complications and why the cascade of events ensues. Until further evidence to guide diagnosis and management is available, an understanding of the expected physiologic derangements is imperative for appropriate treatment of critical illness in asplenic patients.

The astute intensivist must recognize the complexity of sepsis and associated noninfectious complications in the critically ill asplenic patient. The clinician should take appropriate steps to aggressively and systematically implement early appropriate antibiotic therapy, aggressive resuscitation, and hemodynamic support. Failure to respond to this initial therapy should prompt rapid evaluation to identify and address the potential alternate or coexisting ischemic heart disease, RV dysfunction, or thrombosis.

Educating these patients on the nature of their condition and steps they should take to prevent OPSI can substantially reduce their risk of critical illness.

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