Review article

Vascular complications after splenectomy for hematologic disorders

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The most widely recognized long-term risk of splenectomy is overwhelming bacterial infection. More recently, thrombosis has become appreciated as another potential complication of the procedure. Because of these long-term risks, the indications for and timing of splenectomy are debated in the medical community. Accordingly, the adverse effects and benefits of splenectomy for hematologic disorders and other conditions demand further study. This comprehensive review summarizes the existing literature pertaining to vascular complications after splenectomy for hematologic conditions and attempts to define the potential pathophysiologic mechanisms involved. This complex topic encompasses diverse underlying conditions for which splenectomy is performed, diverse thrombotic complications, and multiple pathophysiologic mechanisms. (Blood. 2009;114: 2861-2868)

Introduction

The spleen was once considered unnecessary for life; however, it clearly serves extremely important hematologic and immunologic functions. The spleen is separated into 2 major functional compartments: the white pulp and the red pulp. The white pulp contains a large mass of lymphoid tissue and serves a vital role in the recognition of antigens and production of antibodies. The red pulp of the spleen consists of a tight meshwork of sinusoids, the cords of Billroth, which primarily serve hematologic functions, especially filtration of the blood. The milieu of the red pulp is relatively acidic and hypoglycemic. Aged or damaged red cells not able to tolerate this harsh environment are ultimately removed by splenic macrophages. Antibody-coated cells and bacteria are also recognized and ingested by these phagocytic cells lining the sinusoids. Therefore, persons without a functioning spleen have a severe impairment in their ability to clear encapsulated organisms from the bloodstream. Particulate matter is also removed from red cells as they pass through the splenic sinusoids, and "polished" or "conditioned" red cells, free of surface imperfections, are returned to the bloodstream. The red pulp also acts as a reservoir for approximately one-third of the total platelet mass and a smaller proportion of granulocytes.

Asplenia and hyposplenia

Congenital asplenia can occur in isolation or may be associated with certain forms of congenital heart defects or heterotaxy syndromes.[1] Children with sickle cell disease have acquired hyposplenism that begins at several months of age and progresses to splenic infarction. Young patients with sickle cell disease may also develop recurrent and even life-threatening splenic sequestration requiring surgical splenectomy. Moreover, many immunologic and rheumatic disorders are associated with impairment of the spleen's phagocytic and immunologic functions. Transient functional hyposplenism may also occur during therapy with corticosteroids and after pharmaceutical reticuloendothelial blockade with intravenous IgG or anti-D immunoglobulin.

Surgical splenectomy

According to the National Hospital Discharge Survey, approximately 22 000 total splenectomies were performed for all causes in the United States during 2005.[2] In most institutions, trauma and incidental splenectomy are the primary indications,[3] although splenectomy for trauma is becoming less common than in years past, resulting from more conservative nonoperative management of splenic injury.[4] The most frequent medical indication for splenectomy is a hematologic disorder (Table 1). Splenectomy is performed in patients having hemolytic anemia (eg, hereditary spherocytosis [HS] and autoimmune hemolytic anemia) because the intrinsically abnormal or antibody-coated red blood cells are prematurely destroyed by splenic macrophages. Because splenectomy can ameliorate the underlying anemia, it is often considered the treatment of choice for such conditions. Sickle cell disease may be complicated by splenic sequestration requiring surgical splenectomy, and patients with β-thalassemia may undergo splenectomy to relieve splenomegaly resulting in increased destruction of red blood cells. Splenectomy is also performed in patients with immune thrombocytopenic purpura (ITP), especially when chronic or severe.

Septic risk of asplenia and hyposplenism

For decades, it has been known that in persons with asplenia the major long-term complication is overwhelming bacterial sepsis.[5,6] These infections occur in persons after surgical splenectomy as well as in conditions predisposing to hyposplenism or asplenia. This complication is less frequent than in years past as a result of pneumococcal vaccination, prophylactic penicillin, and prompt administration of parenteral antibiotics when fever occurs.

Table 1. Current indications for splenectomy in hematologic disorders

Hereditary spherocytosis
Other hereditary hemolytic anemias (eg, stomatocytosis, pyropoikilocytosis, pyruvate kinase deficiency)
Sickle cell disease
Thalassemia major or intermedia
Immune thrombocytopenia
Myeloproliferative disorders
Autoimmune hemolytic anemia
Hypersplenism
Lymphoproliferative disorders
Thrombotic thrombocytopenic purpura

Potential vascular complications after splenectomy

An increased risk of vascular complications involving both the venous and the arterial sides of the circulation may result from splenectomy. A vascular complication is defined here as any condition that causes narrowing or occlusion of a blood vessel. This can be a consequence of in situ thrombosis, thromboembolism, vascular smooth muscle remodeling, vasospasm, or atherosclerosis. The risk of thromboembolic events and pulmonary arterial hypertension (PAH) varies greatly depending on the underlying condition for which the splenectomy is performed and whether or not the condition is associated with ongoing intravascular hemolysis (see Table 2). Thromboembolic complications have been most frequently reported after splenectomy in thalassemia intermedia (TI). TI is characterized by chronic intravascular hemolysis and marked ineffective erythropoiesis. In a recent large survey of 8860 patients with thalassemia, the prevalence of thromboembolic events among those with TI was 4%.[7] Remarkably, 94% of these complications occurred after splenectomy. The rate of thromboembolic events in other hematologic disorders after splenectomy has not been thoroughly investigated. The following discussion summarizes these conditions in which vascular complications have been reported and reviews purported pathophysiologic mechanisms.

Table 2. Hypothetical risk of vascular complications based on the presence or absence of intravascular hemolysis and splenic function

Pathophysiologic state	Example	Risk of vascular complications
Neither hemolysis nor splenectomy	Normal person	Baseline*
Hemolysis with intact spleen	Hereditary spherocytosis Glucose-6-phosphate dehydrogenase deficiency β-thalassemia trait Other chronic hemolytic anemia	Baseline* or decreased
Splenectomy without hemolysis	Hereditary spherocytosis† Immune thrombocytopenic purpura Trauma	Increased or baseline*
Splenectomy and ongoing hemolysis‡	Thalassemia intermedia Hgb E/β-thalassemia Sickle cell anemia§ Hereditary stomatocytosis	Greatly increased

*Dependent on the person's unique genetic and environmental risk factors.
†Very mild hemolysis may be present in some persons.
‡Especially intravascular hemolysis.
§Nearly all patients lack functional spleens.

Table 3. Summary of strength of evidence of the cited studies of vascular complications following splenectomy in various hematologic disorders

Medical condition	Reported vascular complications	Strength of evidence
Thalassemia	Arteriothrombosis	Large multi-institutional survey[7,20]
		Individual case reports or small series[21-25]
	DVT or PE	Large multi-institutional survey[7]
		Institutional retrospective review[36,37]
		Individual case reports or small series[38-40]
	PAH	Cross-sectional studies[66,67]
Sickle cell disease*	Arteriothrombosis	Large prospective cohort (stroke)[28]
	DVT or PE	National database review[41,42]
	PAH	Prospective cohort[68]
Hereditary spherocytosis	Arteriothrombosis	Cross-sectional studies[9,10]
		Individual case reports[11]
	DVT or PE	Cross-sectional study[10]
		Individual case reports[46,60]
	PAH	Case control studies[55,56]
		Individual case reports[60,62]
Hereditary stomatocytosis	Arteriothrombosis	Individual case reports[50]
	DVT or PE	Small case series, but includes majority of known cases[17]
		Individual case reports[50]
	PAH	Small case series, but includes majority of known cases[17]
		Individual case reports[50,51,53]
Other asplenic states	Arteriothrombosis	Case control study[8]
		Individual case reports[18,19,26,27]
	DVT or PE	Case control study (autopsies)[43]
		Population-based prevalence study[49]
		Individual case reports[44,45,47,48]
	PAH	Case control studies[55-57]
		Individual case reports[61,63-65]

*None of the reported complications specifically mention their occurrence after splenectomy, yet most patients with sickle cell disease are functionally asplenic.

Table 3 summarizes the cited reports of vascular complications in various disorders along with a description of the strength of the evidence.

Arteriothrombosis

In 1977, a case-control study of 745 World War II servicemen who had splenectomy resulting from trauma demonstrated that they were 1.9 times more likely than controls to die of ischemic heart disease.[8] Twenty years later, Schilling reported a 5.6-fold increased rate of arteriosclerotic events (defined as stroke, myocardial infarction, and coronary or carotid artery surgery) in persons older than age 40 years with HS who had undergone splenectomy compared with persons with HS who had not had splenectomy.[9] This finding was recently confirmed in a follow-up study of arterial events in the same groups of HS patients, which reported a hazard ratio of 7.2 for those with previous splenectomy.[10] Only 7 cases of stroke have otherwise been reported in HS,[11-16] and only one of

these cases clearly followed splenectomy.[11] Otherwise, no documented case reports of myocardial infarction and other forms of atherothrombosis have been described in HS.

Individual reports have described arterial thrombotic events (primarily involving peripheral extremity, pulmonary, and cerebral arteries) after splenectomy in hemolytic disorders other than HS.[17-19] For example, patients with thalassemia have been reported to be at risk of arteriothrombosis after splenectomy, especially ischemic stroke,[20-25] but the incidence appears to be less than with venous events. In the largest series of thrombotic complications in thalassemia reviewing 8860 patients, arteriothrombosis (primarily stroke) was more common in the thalassemia major population (n = 28) compared with TI (n = 9, P = .005) with all but one patient in each group having previously had splenectomy.[7] This difference in prevalence is unclear. In addition, rapidly progressive multi-infarct dementia and acute coronary syndrome have been observed in a series of patients with ITP and previous splenectomy.[26,27] Although stroke is a frequent complication of sickle cell disease,[28] these patients also do not appear to be at increased risk of other forms of atherothrombosis.[29] Interestingly, myocardial infarction and acute coronary syndrome have rarely been reported in thalassemia or any other hemolytic disorders after splenectomy beyond the limited literature in HS.

Venous thrombosis

Local. Acute portal vein thrombosis has been reported after splenectomy for a wide variety of conditions. Indeed, prospective cohort studies reveal that the incidence of thrombosis involving the portal venous system after splenectomy ranges from 5% to 37%, all occurring within 2 months, and the majority within 2 weeks of the surgery.[30-35] This is probably the result of local surgical factors (given that the splenic vein remnant is attached to the portal vein) rather than to the absence of the spleen[30,35] per se. A higher incidence of this complication appears with laparoscopic than with open splenectomy[30] and with greater splenic weight.[30,32,33,35] Higher platelet count shortly after splenectomy does not consistently correlate with this increased risk of thrombosis.[30,33-35]

Systemic. Patients with thalassemia and previous splenectomy appear to have an increased incidence of venous thromboembolism beyond the portal venous system.[7,36-40] Although less commonly reported than in thalassemia, patients with sickle cell disease have also been found to be at increased risk of venous thrombosis.[41,42] In the largest series to date of 8860 patients, 32% of the 146 reported thromboembolic events were deep venous thrombosis, 16% portal venous thrombosis, and 13% pulmonary embolism.[7] In a large review of more than 37 000 autopsies, the odds of fatal pulmonary embolism were 5-fold higher in persons with previous splenectomy (n = 202, performed for any indication) compared with matched controls (n = 403) not having had splenectomy but with comparable trauma or similar surgery.[43] Deep vein thrombosis and pulmonary embolism have also been reported in other conditions after splenectomy.[17,44-49] Patients with hereditary stomatocytosis (whose hemolytic anemia results from abnormalities in red cell cation permeability) are at such a high risk of thrombotic complications after splenectomy that persons with this condition are advised not to undergo the procedure.[17,50-53] The largest series of 7 kindreds with hereditary stomatocytosis (which represents > 50% of the reported cases) includes 13 persons with prior splenectomy, 11 of whom suffered severe, recurrent thromboses (the 2 without thrombosis were still children). Nine of 10 affected persons with intact spleens did not have thromboembolic disease. The reported vascu-

lar events in these patients were all venous, for example, deep vein thrombosis, pulmonary embolism, or portal vein thrombosis.[17]

PAH

Splenectomy appears to be a risk factor for the development of pulmonary hypertension. This is perhaps the most intriguing and frequently reported vascular complication of splenectomy. The classification of pulmonary hypertension has undergone many changes in the past decade and most recently includes a subcategory of PAH in patients with hemoglobinopathies and/or splenectomy (Table 4).[54] The pulmonary hypertension in asplenic conditions, including thalassemia and sickle cell disease, is generally classified as PAH (previously known as primary pulmonary hypertension) or chronic thromboembolic pulmonary hypertension, usually occurring in distal pulmonary arteries and having characteristic histopathology.[55] However, it is possible that the process instead represents "in situ" thrombosis with medial hypertrophy, intimal fibrosis, and plexiform lesions such as seen in idiopathic PAH.[56] In this current review, we will simply refer to all reported types as PAH.

Splenectomy has also been reported as an independent risk factor in patients with PAH referred for lung transplantation[55,56] and in persons with chronic thromboembolic pulmonary hypertension.[57-59] The reported prevalence of splenectomy in patients with PAH ranged from 8.6% to 11.5% compared with 0% to 0.6% in the control groups (patients with other forms of pulmonary disease). It seems probable that the absence of a spleen, not the underlying condition for which the splenectomy was performed, is the primary cause of PAH because the indications for splenectomy in the aforementioned studies were varied, including trauma, ITP, and HS, states where ongoing hemolysis was generally absent, in contrast to disorders where intravascular hemolysis is prominent.[55-57]

In addition to the case-control studies described in the previous paragraph, PAH has rarely been described in individual case reports after splenectomy in HS, hereditary stomatocytosis, myeloid metaplasia, paroxysmal nocturnal hemoglobinuria, and unstable hemoglobinopathies.[17,46,51,53,60-65] In thalassemia patients, after splenectomy PAH occurs at greatly increased frequency (prevalence as high as 70%) over the general population.[66,67] The prevalence of PAH in sickle cell anemia (where the spleen is usually nonfunctional) appears to be approximately 30%.[68] It is important to note that in most studies of sickle cell disease and thalassemia PAH is defined by echocardiographic techniques using a tricuspid regurgitant jet velocity of more than 2.5 m/s as the cutoff for diagnosing PAH. Although this is generally considered to correlate fairly well with right heart catheterization,[69] few studies have included this "gold standard" measurement of PAH in their design, so prevalence data must be interpreted cautiously. Although lack of splenic function has never been directly implicated as its cause, PAH also occurs in various conditions treated with splenectomy, such as

Table 4. Abbreviated World Health Organization Clinical Classification of Pulmonary Hypertension

1. Pulmonary arterial hypertension (PAH)
1.1. Idiopathic (IPAH)
1.2. Familial (FPAH)
1.3. Associated with other underlying disease (including Gaucher disease, hemoglobinopathies, myeloproliferative disorders, splenectomy)
2. Pulmonary hypertension with left heart disease
3. Pulmonary hypertension associated with lung disease and/or hypoxia
4. Pulmonary hypertension due to chronic thrombotic and/or embolic disease
5. Miscellaneous

Adapted from Simmoneau et al[54] with permission.

Gaucher disease,[70,71] or associated with functional hyposplenism, such as sarcoidosis, rheumatoid arthritis, systemic lupus erythematosus, HIV infection, and other autoimmune and immunologic disorders.[69] One case of PAH in isolated congenital asplenia has also been reported.[72] Unfortunately, no published studies have prospectively evaluated the prevalence of PAH in HS or other patients after splenectomy for conditions other than thalassemia or sickle cell disease.

Miscellaneous vascular complications

Leg ulcers and priapism are additional vascular complications that commonly occur in sickle cell disease,[73] and the frequency of these reported events has been correlated with severity of hemolysis.[74] Priapism also occurs in thalassemia and in certain rare hemoglobinopathies, and its prevalence appears to be higher in splenectomized patients.[19,75-78] However, only a limited number of cases of priapism after splenectomy for other indications have been reported.[79]

Animal models of vascular complications after splenectomy

Very few studies describing postsplenectomy vascular complications in animal models have been published. A rabbit model of hemolysis showed evidence of pulmonary platelet thromboemboli occurring only after ligation of the splenic artery.[80] In mouse models of spherocytosis, multiorgan thrombosis and infarction occur at high frequency, although these events occur even with the spleen intact and more probably reflect the extremely high rate of hemolysis.[81,82] To our knowledge, the effect of splenectomy in these murine models has not been evaluated.

Potential pathophysiologic mechanisms of vascular complications after splenectomy

Vascular events after splenectomy are likely multifactorial, probably resulting from some combination of hypercoagulability, platelet activation, disturbance and activation of the endothelium, and altered lipid profiles. The spleen's primary phagocytic function is to remove infectious organisms, other insoluble cellular debris, and senescent or abnormal red cells. This filtration function results from the blood moving slowly through the splenic sinusoids in the red pulp lined with macrophages actively ingesting that which does not easily pass around them. Absence of this extremely sensitive filter may permit particulate matter and damaged cells to persist in the bloodstream, therefore perturbing and activating the vascular endothelium leading to a shift in vascular homeostasis toward enhanced coagulation. There is limited evidence that splenectomy, irrespective of the indication, increases platelet count,[83-87] hemoglobin concentration,[84,87,88] plasma cholesterol,[89-91] leukocyte count,[84] and C-reactive protein levels.[92] Each of these elevations independently is associated with increased risk of arteriothrombosis[93-97] so in combination might be expected to foster a highly unfavorable prothrombotic state.

Lipid alterations

In animal models, altered plasma lipid profiles (combinations of increased total cholesterol, low-density lipoprotein cholesterol and triglycerides, and decreased high-density lipoprotein) after splenectomy have been suggested to contribute to accelerated arteriosclerosis even in the absence of hemolysis.[98,99] These changes were most pronounced in animals after being fed high-fat diets. Similarly,

Caligiuri et al demonstrated that splenectomy in hypercholesterolemic apoE receptor knockout mice accelerated atherosclerosis.[100] The authors proposed that this phenomenon was the result of novel mechanisms in which the splenectomized mice were not able to develop immunity against atherosclerosis. Changes in lipid profiles were not considered to play a large role because cholesterol levels remained constant after splenectomy. Although convincing evidence exists for the presence of hypocholesterolemia in humans with hemolytic anemia,[101-104] it is not clear that splenectomy in these persons results in hypercholesterolemia.[105]

Hypercoagulability

Evidence in thalassemia supports the presence of a hypercoagulable state greatly exacerbated by splenectomy, which is the result of platelet activation,[36,66,106-109] enhanced red blood cell adherence to the endothelium,[110,111] reduced levels of the natural anticoagulants protein C and protein S,[36,112] and increased thrombin generation.[36,86,112] Procoagulant cell-derived microparticles have also been shown to be elevated after splenectomy for hematologic disorders, suggesting that the spleen may play a role in clearing them from the circulation.[113-116] Several studies have reported testing for inherited or acquired thrombophilias at the time of the thrombotic insults, but no consistent risk factor has been shown in a large cohort of splenectomized persons so the contribution of thrombophilia is yet to be determined.[7,30,33,117-119]

It has been hypothesized that the hypercoagulable state after splenectomy may usually be secondary to persistence of abnormal erythrocytes in the circulation, which have been rendered "procoagulant" resulting from increased exposure of phosphatidylserine on the outer membrane surface.[120,121] These abnormal red cells have been shown to be increased in thalassemia and sickle cell disease,[118,122] but not in HS patients.[123] Thrombin generation induced by red cells was increased only in thalassemia patients with prior splenectomy but not in healthy splenectomized persons, suggesting that splenectomy alone was not sufficient to produce these procoagulant erythrocytes.[36] Similarly, erythrocyte fragmentation during hemolysis may lead to formation of microparticles, which also have similar procoagulant properties.[124,125] Therefore, the observed vascular complications after splenectomy in conditions, such as thalassemia and sickle cell disease, may be related to this mechanism, yet it does not explain such complications in other postsplenectomy states without ongoing intravascular hemolysis.

Whole blood viscosity is increased after splenectomy irrespective of indication,[126,127] and in experimental animal models the spleen appears to play a role in maintaining normal hemorheology.[128] This hyperviscosity after splenectomy may be the result in part of the persistence of aged and damaged red cells in the circulation as well as intracellular inclusions, such as Howell-Jolly bodies, siderotic granules, and Heinz bodies, all of which promote decreased erythrocyte deformability.

Pulmonary vascular remodeling

Putative pathophysiologic mechanisms of PAH in patients with hemolytic anemia include platelet and/or endothelial activation induced by asymmetric red blood cell membrane phospholipids[36,122,129] and nitric oxide scavenging by free hemoglobin and subsequent endothelial dysfunction and platelet activation resulting from nitric oxide depletion.[130] Either mechanism may explain PAH in disorders, such as sickle cell disease and thalassemia, where intravascular hemolysis continues despite splenectomy, but not when hemolysis is absent (eg, after splenectomy for trauma) or

when it virtually resolves after splenectomy (eg, as in HS). The consistent factor in PAH affecting such persons with hemolysis is the lack of a spleen. Asplenia may therefore be an important, if not the primary, determinant. Future studies should investigate whether PAH commonly occurs in patients with intravascular hemolysis who have not undergone splenectomy.

Potential protective role of hemolysis with intact spleen

Recently, Schilling et al reported that adult HS patients who had not undergone splenectomy had only 20% the lifetime risk of arteriosclerotic events as first-degree relatives unaffected with HS.[131] This remarkable observation was confirmed in a recent follow-up study in which subjects with HS and prior splenectomy experienced a greater risk of cumulative arteriosclerotic events than HS subjects without prior splenectomy (hazard ratio = 7.15, $P < .001$).[10] However, there was no difference in the frequency of such events between the group with prior splenectomy and their siblings who did not have HS (hazard ratio = 1.56, $P = .11$). Hemolysis in HS before splenectomy occurs almost exclusively in the spleen (ie, extravascularly), so it is possible that their anemia may protect them from thrombotic events in addition to or rather than splenectomy increasing their risk.[131] Most of the literature regarding vascular complications describes conditions with variable degrees of intravascular hemolysis and reduced or absent splenic function, so these several confounders render interpretation of the existing data quite difficult.

Several mechanisms may explain this apparent protection from cardiovascular events in HS and several other hemolytic anemias described below. Patients with hemolysis generally have low plasma cholesterol levels before splenectomy.[101-104] This feature, plus reduced blood viscosity resulting from anemia, may reduce the risk of thrombosis, especially atherothrombosis. Even persons with the β-thalassemia trait appear to have fewer cardiovascular events, possibly resulting from their slightly lower hemoglobin and cholesterol levels.[132-134] Several studies of persons with glucose-6-phosphate dehydrogenase deficiency (a disorder characterized by life-long, intermittent hemolysis that is primarily extravascular) suggest a reduced incidence of cardiovascular events,[135] possibly also the result in part of decreased cholesterol levels.[136,137] In addition, hemolysis leads to increased production of bilirubin, which has antioxidant properties and may protect from cardiovascular disease.[138] To add even more complexity to the subject, persons with sickle cell disease (although clearly at increased risk of PAH, stroke, and peripheral vascular disease) appear to have reduced incidence of atherothrombosis, perhaps resulting from lower cholesterol levels[29,102,139] (Table 2).

Conclusions

There appears to be compelling evidence for a hypercoagulable state after splenectomy performed for various indications. This finding is probably compounded by other underlying conditions,

especially intravascular hemolysis. Although we think there is substantial evidence that PAH and venous thrombosis occur at increased rates in asplenic hosts, the strength of evidence is less convincing that atherothrombosis (including myocardial infarction and stroke) occurs more frequently after splenectomy.

Clinical significance and implications

It is important to better characterize the thrombotic risks of splenectomy in persons without ongoing hemolysis (eg, HS, ITP, trauma) to better define the role of the spleen in vascular homeostasis. PAH in persons with reduced or absent splenic function has a high mortality rate when untreated[140] but may be amenable to novel therapies under development.[141] Greater knowledge about the prevalence, age, and risk factors regarding PAH and other vascular events after splenectomy should assist with the often difficult decision of whether and when splenectomy should be performed in patients with HS, ITP, autoimmune hemolytic anemia, or other conditions for which splenectomy may be beneficial. If validated biomarkers of thrombosis and PAH or actual arterial or venous thrombotic events are indeed problematic after splenectomy, the current practice of recommending splenectomy in many children with HS, for example, may require reassessment. In addition, children and adults who have undergone splenectomy for any reason might be advised to seek monitoring or thromboprophylaxis long after they seem to have been "cured" of their primary condition. Several authors have advocated for the use of short-term and/or long-term thromboprophylaxis after splenectomy, including anticoagulation or antiplatelet agents, especially in thalassemia patients,[36,47,119,142] although no prospective studies have yet evaluated the utility of this approach. Future studies should therefore be directed at better defining the risks of subsequent thrombotic and vascular events accompanying hemolysis, splenectomy, or the combination thereof.

Authorship

Contribution: S.E.C. performed extensive literature review and wrote the manuscript; and G.R.B. assisted in writing and revising the manuscript.

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