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Fatal Venous Thromboembolism After Splenectomy: Pathogenesis and Management

Linda P. Ha, DO
Mark Arrendondo, MD

Venous thromboembolism (VTE) occurs in approximately 10% of patients after splenectomy, particularly splenectomy performed for hematologic abnormalities. Clinicians often fail to recognize this potential complication in the postoperative period, leading to inappropriate anticoagulation prophylaxis and treatment for these patients. The authors discuss the pathophysiologic mechanisms of VTE in patients who undergo splenectomy and offer management strategies for this complication. A case report of a patient who underwent splenectomy for idiopathic thrombocytopenia purpura, with subsequent fatal VTE, highlights the importance of this issue. The authors also review current guidelines for managing venous thromboprophylaxis in patients who undergo general, laparoscopic, and cancer-related surgical procedures, and they compare these patients to those who undergo splenectomy.

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The risk of postoperative venous thromboembolism (VTE) in patients who undergo general surgical procedures without thromboprophylaxis ranges from 15% to 40%, with a rate of fatal pulmonary embolism of 0.2% to 0.9% in these patients.[1] Without thromboprophylaxis, the risk for symptomatic VTE is highest within the first 2 weeks after surgery, and the risk for fatal postoperative pulmonary embolism is highest within 3 to 7 days after surgery.[2] Approximately 10% of symptomatic VTE cases occur within 3 months of hospital discharge.[2] Despite guidelines established in 2008 by the American College of Chest Physicians (ACCP), VTE, specifically pulmonary embolism, remains the primary cause of preventable death in patients who undergo surgical procedures, and it remains a matter of concern for all hospitalized patients.[1,2]

The National Quality Forum, The Joint Commission, the Surgical Care Improvement Project, and the Agency for Healthcare Research and Quality have all made VTE recognition and management a performance measure for physicians and hospitals. In 2008, the Centers for Medicare and Medicaid Services designated VTE as a "hospital-acquired condition" for the purposes of hospital reimbursement.[3] Also in 2008, *The Surgeon General's Call to Action to Prevent Deep Venous Thrombosis and Pulmonary Embolism* was published.[4] That initiative emphasized the need for increased physician awareness of VTE, evidence-based practices for patients with deep venous thrombosis (DVT), and more research on the causes, prevention, and management of VTE. The National Quality Forum currently endorses 6 standards targeting VTE, all of which are stewarded by The Joint Commission.[5-9]

In the present article, we offer a case report and clinical vignette that highlight morbidity associated with VTE after surgery—specifically after splenectomy procedures. Our objective is to raise physician awareness of the unique VTE risks that splenectomy surgical procedures pose to patients.

Report of Case

A 44-year-old white man presented to our institution in 2010 for an elective splenectomy after recurrence of splenosis, a condition characterized by regeneration of splenic tissues following previous splenectomies. The splenosis had resulted in refractory thrombocytopenia, leading to the patient's decision to undergo the surgical procedure.

The patient's medical history was notable for stage-1 lymphocyte-dominant Hodgkin lymphoma, which had been diagnosed in 2003 and had been in remission since initial radiation therapy. In 2007, he was diagnosed as having idiopathic thrombocytopenia purpura (ITP), leading to his first splenectomy. After this splenectomy, acute DVT (involving the left popliteal, left peroneal, and left soleal veins) developed in the patient, and he received antico-

From Summa Health Systems in Akron, Ohio.

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Address correspondence to Linda P. Ha, DO, Associate Director, Internal Medicine Center, Summa Health Systems, 55 Arch St, Suite 1A, Akron, OK 44304-1424.
E-mail: hal@summahealth.org.

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agulation with dalteparin sodium. In 2009, after his second splenectomy for splenosis, acute DVT (involving the left popliteal and left peroneal veins) again developed, and the patient was treated with low molecular weight heparin (LMWH).

In 2010, in preparation for the patient's third splenectomy, again for splenosis, a retrievable inferior vena cava (IVC) filter was placed. Use of LMWH continued until 2 days before surgery. An open splenectomy procedure was performed 15 days after IVC filter placement. Postoperatively, the patient was placed on heparin (5000 U subcutaneously every 12 hours) for "DVT prophylaxis." On postoperative day 4, the patient complained of epigastric pain and persistent calf pain. He had a cardiopulmonary arrest several hours after these symptoms.

During the resuscitation attempt, 2-dimensional echocardiographic examination revealed multiple masses within the right atrium, consistent with pulmonary embolism and acute right ventricular dysfunction. Autopsy showed multiple, bilateral pulmonary embolisms. The IVC filter was located, with adherent thrombi. At death, the patient's platelet count was 156,000/μL.

Prophylaxis in Patients Undergoing Surgical Procedures

Lack of adherence to guidelines, inadequate use of venous thromboprophylaxis regimens, and variations in practice among subspecialists have all been cited as reasons why VTE remains a clinically significant problem in patients undergoing surgical procedures. Physicians often select the type and duration of anticoagulation thromboprophylaxis in the perioperative period on the basis of risk stratification for the patient and the particular surgical procedure being performed. Currently, patients undergoing general surgical procedures are stratified as being at high risk (odds ratio [OR], >10), moderate risk (OR, 2-9), or minor risk (OR, <2) for perioperative VTE on the basis of multiple risk factors.[10] High-risk patients include those having either abdominal or thoracic surgical procedures or those who have experienced trauma. Moderate-risk patients include those with malignancy, congestive heart failure, or previous VTE. Minor-risk patients are those who are obese or immobile or who are aged 45 years or older (eg, patients aged 45 to 49 years have an OR of 1.5 for VTE, compared with that of younger patients).[10]

Other factors that contribute to increased risk for VTE in patients undergoing surgical procedures include the type of anesthesia, duration and type of surgical procedure, and postoperative infection.[1] Major general, major gynecologic, major urologic, and neurologic surgical procedures have a similar DVT prevalence, ranging from 15% to 40% in patients not receiving thromboprophylaxis. Orthopedic surgical procedures are of the highest risks for VTE, with the rate of 40% to 60% among patients without thromboprophylaxis.[1] The 2008 ACCP guidelines include recommendations for venous thromboprophylaxis in patients needing surgical procedures on the basis of the patient's risk factors and type of surgical procedure.[1] These recommendations recognize the necessity of balancing considerations of VTE prevalence with the risk of bleeding from using anticoagulants.[1]

Despite such guidelines, lack of adherence remains a problem. The ENDORSE trial[11] showed that nearly 30% of at-risk patients undergoing surgical procedures did not receive thromboprophylaxis as recommended by the ACCP. Similarly, a more recent study[12] noted underuse of VTE prophylaxis after many types of surgical procedures—as well as the finding that, when thromboprophylaxis was used, the type, dose, and duration of prophylaxis did not usually comply with ACCP guidelines. That observational study of 1897 patients who had a surgical procedure showed appropriate prophylaxis—with correct dose, type, and duration—in only 32% of cases, with inadequate duration of prophylaxis in 11% of the patients undergoing general surgical procedures. A 2008 analysis by Schackford et al[13] of approximately 38,000 patients using surgical services suggested that 84% of patients received at least partial compliance to ACCP guidelines for venous thromboprophylaxis. That analysis also showed that complete omission of prophylaxis was responsible for 47% of the preventable cases of VTE, and nearly 40% of these VTE cases were considered preventable.

The patient in our case presentation was considered at high risk for perioperative VTE, not only on the basis of the type of surgical procedure (ie, abdominal), but also on the basis of his history of malignancy and previous DVT. The resumption of a full-dose anticoagulation treatment regimen in patients with preexisting anticoagulation indications should be performed if there are no contraindications.

Special Considerations for Prophylaxis in Patients With Cancer

Because most patients who undergo splenectomy have concomitant malignancies, the risk for VTE is inherent not only to the surgical procedure itself, but also to the persistent hypercoagulable states of malignancies. There are no venous thromboprophylaxis guidelines that target patients with cancer who undergo splenectomy. Thus, treatment of those patients must rely on current knowledge about VTE prophylaxis in patients who undergo general surgical procedures.

Thromboprophylaxis in patients with malignancies and hematologic conditions who undergo surgical procedures involves great challenges, primarily because hypercoagulable states among these patients lead to increased risk of VTE during the postoperative period. One study[14] found that approximately 12% of all patients with cancer had VTE during their illnesses.[14] The risk of VTE is 4 to 5 times

greater in patients with cancer who undergo surgical procedures, compared with those who do not have surgical procedures.[15]

Several factors have been shown to increase the risk of VTE in patients with cancer during the postoperative period. The need for perioperative blood transfusions, particularly in women, has been associated with a 2-fold increased risk of VTE, compared with individuals who do not need transfusions.[15] Other risk factors for VTE include age (ie, >40 years), thrombophilia, cancer procoagulants, duration and complications of cancer, debilitation, and slow recovery. Despite anticoagulant prophylaxis, patients with cancer have twice the risk of postoperative VTE and a 3% increased risk of death, compared with individuals without cancer.[15] The ENOXACAN trial[16] and the Canadian Colorectal Surgery DVT Prophylaxis trial[14] both showed the rate of VTE to be between 9% and 18% among patients with cancer undergoing surgical procedures—even if the patients received LMWH or unfractionated heparin (UFH) prophylaxis.

The ACCP recommends using UFH (5000 U 3 times daily) or high-dose LMWH (>3400 U daily) for venous thromboprophylaxis in patients with cancer.[17,18] Studies[14,16] have found no statistically significant differences in VTE incidence or bleeding between UFH and LMWH prophylaxis in patients with cancer who require surgical procedures. The American Society of Clinical Oncology has extended its recommendation for using fondaparinux sodium for both VTE prophylaxis and treatment. Both the ACCP and the American Society of Clinical Oncology recommend the use of LMWH for 4 weeks in patients who have had major abdominal or pelvic cancer-related surgical procedures or who have other "high-risk features" (eg, residual malignancy after surgical procedure, obesity, previous VTE).[19,20] Other medical societies have similar recommendations.[21] No studies, to our knowledge, have evaluated UFH or fondaparinux for extended VTE prophylaxis. The optimal duration for venous thromboprophylaxis for patients who have had splenectomies is still unclear.

Venous Thrombosis After Splenectomy

The overall incidence of VTE, including DVT and pulmonary embolism, ranges from 12% to 29% among patients who have undergone splenectomies.[22,23] Splenectomy may be performed as either an open procedure or a laparoscopic procedure. Laparoscopic splenectomy is preferred over the open approach because of a shortened recovery time and fewer complications. A retrospective analysis[24] of 49 patients who had splenectomy for ITP showed a 10% incidence of venous thrombosis after either open or laparoscopic procedures—if no prophylactic anticoagulations were administered.

Despite similar venous thrombosis incidence rates between patients who have had open surgical procedures vs laparoscopic procedures, the risk of venous thrombosis after laparoscopic splenectomy has been found to be greater compared with risks from other laparoscopic surgeries.[25,26] This risk is especially high compared with rates from other, general abdominal surgical procedures. A retrospective analysis[10] of 375,748 patients who had major abdominal surgical procedures showed that patients who underwent splenectomy for any indication had the highest risk for VTE (OR, 2.69), and the VTE risk was highest among patients aged 45 to 49 years (OR, 1.5).

Concerns about postoperative infection and bleeding after splenectomy often take precedence over concerns about VTE among physicians. Studies have found that nearly 14% of surgeons who perform splenectomy do not apply appropriate perioperative VTE prophylaxis,[27] compared with 85% adherence to postoperative pneumococcal vaccination.[28]

Hypercoagulable Conditions Associated With Splenectomy

Procoagulant Cell-Derived Microparticles

Besides having hematologic and immunologic functions, the spleen plays a crucial role in the clearance of cells that express procoagulant cell-derived microparticles (C-MPs) on their surfaces. When red blood cells become damaged, they express negatively charged procoagulant phospholipids on their surfaces as signals for cell removal and apoptosis. These cells are capable of interacting with other cells, leading to thrombosis, inflammation, and angiogenesis.[29]

The expression of annexin V binding sites and tissue factors makes C-MPs highly procoagulant, and C-MPs have been found to be sensitive biomarkers of both prothrombotic and inflammatory conditions.[30] Phosphatidylserine, an anionic phospholipid that is expressed on C-MPs, signals for clearance by macrophages. The spleen is the main organ that removes cells that have phosphatidylserine in their membranes. One study[31] noted an increase in plasma levels of thrombin-antithrombin III complex (TAT) among splenectomized patients with hemoglobin E disease or thalassemia, leading to in vivo coagulation activation. The authors concluded that the increased TAT levels were a result of the increased number of circulating red blood cells exposed to phosphatidylserines after splenectomy.[31] Accumulation of these phosphatidylserine-exposed cells lead to increased risk of thrombosis.

Several C-MPs have been implicated in the increased risk of thrombosis among splenectomized patients, most of which are also found in patients with ITP. These C-MPs include red cell microparticles (RMPs), leukocyte microparticles (LMPs), endothelial microparticles (EMPs), and platelet microparticles (PMPs).[30] Red cell microparticles are associated with increased clotting factor activities and

a shortened partial thromboplastin time (PTT).[30] Leukocyte microparticles are derived from monocytes and neutrophils and are the main source of tissue factors, which have been implicated in the progression of atherosclerosis.[30] Endothelial microparticles have been shown to be a biomarker of endothelial injury, and some EMPs carry von Willebrand factors, resulting in coagulation and inflammation. Furthermore, EMPs have been linked to atherosclerosis and progression of vascular disorders. High levels of PMPs have been associated with transient ischemic attacks in 19% of patients with ITP.[32] Platelet microparticles can also bind and activate neutrophils, leading to the suggestion that PMPs have a role in inflammation and angiogenesis.[30]

Antiphospholipid Antibodies

Antiphospholipid antibodies (APLAs) have been found to be elevated in patients with ITP who have intact spleens. In 1 study,[33] researchers found APLAs in approximately 30% of patients with ITP, although other studies[32,34] have reported rates ranging from 30% to 73% for the incidence of APLAs in patients with ITP. Bidot et al[32] found that 67% of their patients with ITP had at least 1 type of APLA (either IgG or IgM), and that 25% of their patients who had any thrombosis also had APLAs. However, none of the patients in that study had lupus anticoagulant. The authors proposed that some APLAs bind and activate platelets to induce thrombocytopenia, while other APLAs bind to phospholipid membranes to interfere with platelet functions.[32]

Bidot et al[32] showed that the APLA subclass of anti–β_2 glycoprotein 1 autoantibodies, which were detected in 19% of patients with ITP, induced platelet activation and shedding of PMPs. The incidence of arterial thrombosis, particularly transient ischemic attacks and coronary artery thrombosis, was more common than VTE in patients with APLAs. Levels of APLA were noted to rise with exacerbation of ITP and decline or disappear during remission. Furthermore, the rise in APLA levels during ITP exacerbation was associated with clinical bleeding—more so than with thrombosis.[32]

The clinical significance of APLAs in patients with ITP remains controversial. Some studies have reported that antiphospholipid syndrome developed within 5 years in nearly half of patients with ITP and persistently high levels of APLA.[35]

Protein C and Protein S

There is little indication that deficiency in protein C or protein S develops in patients after splenectomy surgical procedures. There have been reported cases of decreased levels of protein C and S and elevated levels of thrombin-antithrombin complex in patients who have undergone splenectomy, but most of those cases were associated with liver dysfunction. Decreased levels of these proteins do not fully explain the hypercoagulable states following splenectomy.

Heighten Thrombosis Risk With Thalassemia?

Studies of patients with thalassemia who underwent splenectomy have led to insights into the possible pathogenesis of hypercoagulable conditions after surgical procedures. Nearly one-third of patients had either DVT or pulmonary embolism after splenectomy for β-thalassemia intermedia.[30]

Several factors have been identified as causes of thrombosis among these patients. The expression of phosphatidylserine on thalassemic red blood cells has been shown to result in procoagulant effects in patients with thalassemia, and the thrombosis risk is heightened after splenectomy because of the inability to clear these cells from the body.[36] Heightened thrombin formation, damaged red blood cell membranes, thrombocytosis, and spontaneous platelet aggregation and activation are other mechanisms proposed for the increased risk of thrombosis after splenectomy in patients with thalassemia.[22] Furthermore, a low-grade consumption coagulopathy has also been observed among β-thalassemia and hemoglobin E patients who had blood transfusions before undergoing splenectomy.[37]

Thrombocytosis as Cause of VTE After Splenectomy?

Postoperative thrombocytosis has been found in 3% to 13% of patients who had splenectomy.[22] Essential thrombocytosis carries a higher risk for both venous and arterial thrombosis compared with secondary thrombocytosis (12.4% vs 1.6%, respectively)—especially after splenectomy.[38] By contrast, case reports described by Mohren et al[23] revealed no direct correlation between postsurgical platelet counts and development of venous thrombosis. However, the 1 patient in whom bilateral pulmonary embolism developed despite extended use of LMWH prophylaxis (for 35 days postoperation) had a platelet count of $1.156 \times 10^3/\mu L$ at the time of diagnosis.

There is a correlation between thrombosis and postsurgical thrombocytosis. In individuals with myeloproliferative disorders, platelet counts of greater than $1000 \times 10^3/\mu L$ after splenectomy were associated with a 3% to 4% risk for thrombosis, compared with a 7% risk for thrombosis in patients with postsplenectomy thrombocytosis after surgical procedures for myeloid metaplasia.[23] In 1 study,[39] thrombosis was seen in 3% to 4% of patients with platelet counts greater than $1000 \times 10^3/\mu L$ including 57 patients who had reactive thrombocytosis. In a retrospective study[40] of 80 patients who underwent splenectomy for sideroblastic anemia, hemolytic anemia, hemoglobinopathies, or thalassemia, 13% of patients had thromboembolic complications in association with persistent postsplenectomy thrombocytosis.

Despite these correlations between postsplenectomy

thrombocytosis and thrombosis, the pathophysiologic mechanisms of this association remain controversial. One proposed mechanism involves spontaneous platelet activation and aggregation after splenectomy, as observed in patients with thalassemia.[22] Other proposed mechanisms for the increased risk of postsplenectomy thrombosis include elevated levels of serum interleukin-6, tumor necrosis factor, and C-reactive protein, as well as in vivo platelet activation and platelet hyperaggregation.[41]

Given the correlation between postsplenectomy thrombocytosis and thrombosis, some authors have advocated adding antiplatelet agents to treatment for splenectomized patients with platelet counts greater than $1500 \times 10^3/\mu L$ only if there are additional cardiovascular risk factors. Currently, there are no guidelines on recommendation of routine use of venous thromboprophylaxis in patients who have undergone splenectomies and who have thrombocytosis. In *Table 1*, the procoagulant factors that have been associated with hypercoagulable states after splenectomy are summarized.

Sites of Thromboembolism After Splenectomy

In addition to risks for DVT and pulmonary embolism, patients who have undergone splenectomy are at increased risks for venous thrombosis within the portal, splenic, and mesenteric veins. The incidence of portal and splenic vein thrombosis (PSVT) after splenectomy is highly variable. Portal or mesenteric vein thrombosis is associated with a 5-fold increase in mortality beyond the first year of surgical procedures among patients who had splenectomy for nonmalignant causes. One study[42] reported a 52% incidence of PSVT among 33 consecutive patients who had laparoscopic splenectomy. The authors proposed a positive correlation between spleen weight (median weight, 218 g) and PSVT. Among the patients with ITP in that study, 30% had intrahepatic portal vein thrombosis, and none had complete splenic vein thrombosis. Patients with hematologic diseases tended to have a higher incidence of portal vein thrombosis after splenectomy.[43]

A Dutch study[44] reported portal vein thrombosis in 10% of patients with hematologic diseases, compared with 2% among patients with nonhematologic disease states. Other investigators have reported that among the 8% of their patients with portal vein thrombosis, 74% had hematologic disease, and the thromboses occurred as late as 3 years after splenectomy.[23] Autoimmune hemolytic anemia and myeloproliferative syndromes are also commonly associated with increased risk for portal vein thrombosis. The combination of myeloproliferative disease and splenomegaly (spleen weight >3000 g) was associated with a 75% incidence of portal vein thrombosis.[23] Mesenteric vein thrombosis tends to occur in patients with concomitant hypercoagulable states, such as deficiencies in protein C, protein S, or antithrombin III.

Surveillance for PSVT After Splenectomy

The majority of patients with PSVT are asymptomatic, or they have nonspecific symptoms. Because the incidence of PSVT is highly variable after splenectomy surgeries, postoperative surveillance to screen for PSVT is either discouraged or difficult to standardize for patient selection. Fever, with a temperature greater than 38°C, after postoperative day 2 was the only reliable indicator for possible PSVT in 1 study.[42]

A prospective study by Cappellini et al[22] reported the incidence of postsplenectomy PSVT to be 6% to 10%, as determined by ultrasonography screening, although computed tomography studies reported incidence rates to be as high as 52%. Color Doppler sonography, contrast-enhanced color Doppler sonography, contrast-enhanced ultrasonography, computed tomography, and magnetic resonance imaging using second-generation contrast agents have all been effective modalities for detecting portal and mesenteric venous thrombosis.

PSVT and Laparoscopic Splenectomy Surgical Procedure

Laparoscopic splenectomy has been shown to have a higher risk for both portal and mesenteric venous thrombosis, compared with open splenectomy. Ikeda et al[42] reported a 50% increased risk of PSVT in patients who had a laparoscopic surgical procedure vs open splenectomy. Several mechanisms have been proposed for this greater risk.[38] First, the increased venous stasis caused by carbon dioxide pneumoperitoneum during a laparoscopic procedure results in a reduction in the pressure-mediated portal vein flow. Second, the dissection of the pancreatic tail from the retroperitoneum for endoscopic stapling is minimal and can result in a large residual stump of the splenic vein. Venous stasis in the splenic stump is believed to increase the risk for PSVT among these patients.

There is currently no consensus for screening patients for portal or mesenteric venous thrombosis after splenectomy. Even if screening is considered, there is no established time when it should be performed. Maintaining a high clinical suspicion and monitoring for abdominal symptoms after splenectomy may be the best practice for detecting portal or mesenteric venous thrombosis.

Prevention of Thromboembolism in Patients Who Have Undergone Splenectomy

Concerns about intraoperative and postoperative bleeding with splenectomy greatly influence venous thromboprophylaxis practices during the perioperative period. Because some splenectomy procedures are performed with trauma patients, perioperative anticoagulation prophylaxis is often contraindicated or delayed. Postoperative bleeding after laparoscopic splenectomy occurs in approximately 3% of patients.[39]

Table 1.
Procoagulant Factors Associated With Asplenia[30-32]

Procoagulant	Characteristics	Proposed Hypercoagulable Mechanism With Asplenia
Cell-Derived Microparticles (C-MP) Annexin V binding sites Phosphatidylserine (PS) Red cell microparticles (RMP) Leukocytes microparticles (LMP) Endothelial microparticles (EMP) Platelets microparticles (PMP)	Negatively charged phospholipids expressed on damaged red blood cells signaling for cell removal and apoptosis. PS is an anionic phospholipid expressed on C-MP. LMP is derived from monocytes and neutrophils. EMP is a biomarker of endothelial injury and some EMP carries von Willebrand factors. PMP binds and activates neutrophils.	PS signals clearance of red blood cells by macrophages. RMP is associated with increased clotting factor activities and shortened partial thromboplastin time. LMP is the main source of tissue factor and implicated to atherosclerosis progression. EMP leads to coagulations, inflammation, atherosclerosis, and vascular disorders. PMP is associated with transient ischemic attacks, inflammation, and angiogenesis.
Thrombin-Antithrombin III Complex	Increased levels are seen in hemoglobin E/β-thalassemic patients who have undergone splenectomy and have hemoglobin E or β-thalassemia.	In vivo coagulation activation. Increased level of thrombin-antithrombin III complex may be the result of an increased number of circulating PS-exposed red blood cells.
Antiphospholipid Antibody (APLA)	Increased levels of APLA are seen mostly in immune thrombocytopenic purpura with intact spleen. APLA levels rise with idiopathic thrombocytopenia purpura exacerbation.	Either IgG or IgM can be present. APLA binds and activates platelets to induce thrombocytopenia or binds to phospholipid membranes to interfere with platelet functions. Anti-β2GP1 induces platelet activation and shedding of PMP. Arterial thrombosis (transient ischemic attacks and coronary thrombosis) are more common than venous thrombosis.
Protein C and S	Deficiency is uncommon with splenectomy but reported cases have been associated with liver disease.	Spontaneous platelet activation and aggregation.
Platelets/Thrombocytosis[a]	Patients with essential thrombocytosis had higher risk for both venous and arterial thrombosis after splenectomy. Thrombosis has been found to be more common in patients with myeloproliferative disorder or myeloid metaplasia.	
Other Serum interleukin 6 Tumor necrosis factor C-reactive protein		Increased levels after splenectomy.

[a] Most studies noted platelet count of more than 1000 X $10^3/\mu L$ to be associated with thrombosis.

Several recommendations to avoid perioperative bleeding after anticoagulation initiation have been proposed. Initiation of enoxaparin sodium injection is recommended 12 to 24 hours after a knee replacement surgical procedure, but it is appropriate to initiate 2 hours before a major abdominal surgical procedure.[45] Dalteparin can also be started 1 to 2 hours before a major abdominal surgical procedure. By contrast, fondaparinux injection is recommended to be started 6 to 8 hours after a major abdominal surgical procedure.[43] Therefore, initiation of venous thromboprophylaxis with anticoagulants for patients undergoing major abdominal surgical procedures appears to be safe when started before the procedure and is warranted for high-risk patients.

Although patients who undergo splenectomy share some postoperative venous thrombosis risks with other patients having major abdominal surgeries, the risks of bleeding and comorbidities (eg, malignancies, trauma, sepsis), as well as the hypercoagulable states unique to asplenia, pose substantial challenges to venous thromboprophylaxis management. All of these factors should be considered in the selection of the type and duration of VTE prophylaxis for splenectomized patients.

The following discussion incorporates current guidelines of VTE management and offers management strategies for patients after splenectomy.

Venous Thromboprophylaxis Guidelines

The ACCP supports the use of LMWH, low-dose UFH, and fondaparinux for venous thromboprophylaxis in patients undergoing a laparoscopic surgical procedure of any type.[1] This recommendation, however, does not delineate between different laparoscopic indications (eg, cholecystectomy vs splenectomy) or their respective thrombosis risks (eg, traumatic vs hematologic malignancies).

Until more specific recommendations are available for laparoscopic splenectomy surgical procedures, the current ACCP recommendations provide a reasonable foundation on which to base prophylaxis strategies for patients undergoing splenectomy.[1] However, additional considerations must be made for traumatic vs hematologic or cancer cases. Furthermore, risks for PSVT and mesenteric venous thrombosis, as well as DVT and pulmonary embolism, must be considered.

Interrupted Inferior Vena Cava Filters

The use of a retrievable IVC filter for the prevention of thromboembolism is common in patients experiencing trauma and in patients for whom anticoagulation is contraindicated because of increased risk of bleeding. Although a comprehensive review of IVC use is beyond the scope of the present article, several key issues deserve attention as they apply to patients who have undergone splenectomy.

Venous thromboprophylaxis with an IVC filter has been shown to protect against pulmonary embolism but not against DVT. The PREPIC trial[46] and its subsequent 8-year follow-up study[47] found that IVC filters reduced the risk of pulmonary embolism but increased the incidence of DVT, without affecting mortality. The ACCP guidelines[1] recommend venous thromboprophylaxis with LMWH for patients who have major trauma and no contraindications, but the guidelines do not recommend the use of IVC filters as thromboprophylaxis. Congruent with the PREPIC findings,[46,47] the ACCP guidelines support use of IVC filters in patients with acute proximal DVT to prevent pulmonary embolism when anticoagulation is contraindicated.

The use of IVC filters for venous thromboprophylaxis and DVT treatment in patients with cancer remains controversial. The placement of IVC filters in patients with cancer has not been shown to result in survival benefits, and in some cases, patients had lower survival rates after IVC filter placement.[46] Therefore, for selected patients who undergo splenectomy as a result of major trauma and who do not have contraindications to anticoagulation, LMWH appears to be the preferred venous thromboprophylaxis regimen. The use of IVC filters should be reserved for patients in whom bleeding is a concern. When splenectomy is performed for malignancy-related conditions, anticoagulants are preferable to IVC filters for venous thromboprophylaxis. The *Figure* highlights indications for IVC filter placement, with special attention to conditions associated with splenectomy.

Anticoagulation

Anticoagulants—specifically warfarin, LMWH, and UFH—have all been shown to be effective for venous thromboprophylaxis for both surgical and general medical patients. We focus here on the role of VTE prophylaxis with anticoagulation in patients who have had surgical procedures for cancer, as well as the potential implications for patients with cancer who have undergone splenectomy.

The CLOT investigators[51] showed that LMWH (dalteparin, 200 IU/kg once daily) was more effective than oral anticoagulants (warfarin or acenocoumarol) in preventing recurrent venous thrombosis, without increasing the risk of bleeding, among patients with cancer who did not have surgical procedures. Eleven percent of the patients in that study had hematologic cancer.[51] The ENOXACAN study[16] showed that LMWH (enoxaparin sodium, 40 mg daily) had a better rate (though not statistically significant) than UFH (5000 U 3 times daily) of decreasing thromboembloic complications (15% frequency vs 18% frequency, respectively) among 631 evaluable patients who underwent elective curative cancer surgical procedures involving the abdomen and pelvis.

The discovery of an antitumor effect with LMWH further favors its use for patients with malignancies, both as primary venous thrombosis prevention and VTE management. Tinzaparin sodium has been shown to inhibit colon and lung carcinoma-induced angiogenesis, tumor growth, and tumor regression.[52] Other possible antineoplastic mechanisms of LMWH include the inhibition of coagulation factors, growth factors, proteases, and oncogene expression, as well as effects on oxygen-free radicals and stimulation of immune competence, cell differentiation, and apoptosis.[51]

Prophylaxis

- Trauma,[48] major or multiple
- Prolonged immobilization
- Major surgery in patients with suspected hypercoagulable states or patients with remote history of deep venous thrombosis or pulmonary embolism
- Advanced malignancy[48] (especially with chemotherapy)
- Contraindication or complication of anticoagulation[49]
- Bleeding disorders or clinically significant thrombocytopenia (<50,000 platelets/μL)

Treatment

- Extensive deep venous thrombosis[50]
- Deep venous thrombosis or pulmonary embolism[1]

Figure. *Indications for placement of retrievable inferior vena cava filters, with special considerations for patients who have undergone splenectomy.*

Table 2.
Venous Thromboprophylaxis Recommendations for Major General, Laparoscopic, and Cancer-Related Surgical Procedures

Modality	Surgical Procedure		
	Major General	Laparoscopic	Cancer-Related
Unfractionated Heparin	Low dose unfractionated heparin (LDUH) 3 times daily (Grade 1A[a]) for moderate and high-risk patients LDUH 3 times daily combined with mechanical method and/or intermittent pneumatic compression for patients with multiple risk factors (Grade 1C[a])	LDUH for patients with additional VTE risk factors (Grade 1C[a]) Gynecology patients with additional VTE risk factors (Grade 1C[a])	Gynecologic cancer: LDUH 3 times daily (Grade 1A[a]) or LDUH combined with GCS or IPC (Grade 1C[a]) LDUH 5000 U 3 times daily[16]
Low Molecular Weight Heparin (LMWH)	For both moderate-risk and high-risk patients undergoing major surgical procedure (Grade 1A[a]) and patients with multiple risk factors (combined with mechanical method and/or pneumatic stockings (Grade 1C[a])	For patients with additional VTE risk factors (Grade 1C[a]) Gynecology patients with additional VTE risks (Grade 1C[a])	Gynecologic cancer: (Grade 1A[a]) LMWH (>3400 U/d) (Grade 1A[a]): either dalteparin (5000 U/d) or enoxaparin (40 mg/d) Postdischarge prophylaxis for 28-30 d (Grade 2A[a]) 4 weeks after discharge for major abdominal/pelvic surgical procedures with residual malignant disease, obesity, and previous history of VTE[20]
Mechanical Prophylaxis	Recommended for patients undergoing general and abdominal-pelvic surgical procedures who are at low risk for VTE (Grade 2C[a]), moderate risk for VTE (Grade 2C[a]), and high risk for major bleeding (Grade 2C[a]), with IPC being preferable for patients with moderate or high risk or when heparin anticoagulation is contraindicated (Grade 2C[a]). Elastic stocking or IPC should be added to pharmacologic prophylaxis for patients at high risk for VTE (Grade 2C[a]).[55]	Either GCS or IPC is recommended for patients with additional risk factors (Grade 1C[a])	Gynecologic cancer: GCS or IPC combined with either LMWH or LDUH (Grade 1C[a]) or IPC started before surgical procedure and continuous until ambulation (Grade 1A[a])
Other Anticoagulants	Fondaparinux for high-risk patients undergoing major surgical procedure for cancer (Grade 1A[a]) or combined with GCS and/or IPC (Grade 1C[a])	Fondaparinux (Grade 1C[a]) if there are additional risk factors[1]	Gynecologic cancer: Fondaparinux (Grade 1C[a]) Fondaparinux 2.5 mg daily for 5-9 d[53] Danaparoid[54]
Inferior Vena Cava Filter (IVC)	Not recommended for trauma patients as thromboprophylaxis (Grade 1C[a]) Indicated as thromboprophylaxis for major trauma with significant VTE risk when anticoagulants are contraindicated[49] Patients having major surgery within 2 weeks of an acute proximal deep venous thrombosis or pulmonary[48] embolism		Not routinely recommended for thromboprophylaxis Associated with increased risk of both pulmonary embolism and deep venous thrombosis No survival benefit when compared with anticoagulation

[a] Grade 1A, stong recommendation, high-quality evidence; Grade 1C, low- or very low-quality evidence; Grade 2C, weak recommendation, low- or very low-quality evidence.[19]

Abbreviations: GCS, graduated compression stockings; IPC, intermittent pneumatic compression; VTE, venous thromboembolism.

Table 2 highlights various venous thromboprophylaxis regimens that are commonly used in patients undergoing major general, laparoscopic, and cancer-related surgical procedures. Unfortunately, studies on VTE after splenectomy have used variable types, doses, and durations of LMWH. Prophylaxis of VTE with dalteparin (5000 IU daily or 2500 IU twice daily for a median of 7 days) was shown to be effective in a series of patients who had splenectomy for various reasons, and prophylactic low-dose warfarin was shown to be insufficient in preventing portal venous thrombosis.[23] Therefore, LMWH appears to be preferable to low-dose warfarin and UFH for VTE prophylaxis in patients after splenectomy. However, more research is warranted on the optimal dose for LMWH.

Conclusion

Asplenia produces a unique hypercoagulable state that increases the risk for venous thrombosis, including thrombosis of the mesenteric, portal, and splenic veins. Abdominal pain and fever may be the only indicators of mesenteric, portal, and splenic venous thrombosis. Splenectomy for hematologic cancer, splenomegaly, and laparoscopic splenectomy are associated with increased risk of venous thrombosis, particularly for portal and splenic vein thrombosis. Anticoagulation with LMWH for an extended period (ie, 30 days postoperatively) may be a beneficial prophylaxis regimen in selected patients.

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