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Overview for Venous Thromboembolism: New Perspectives

THE CURRENT ISSUE of *Seminars in Vascular Surgery* deals with an increasingly recognized medical problem that affects surgical and medical patients alike. The problem of deep vein thrombosis (DVT), which is the etiology and nidus for venous thromboembolism (VTE), is commonly the result of environmental factors such as trauma, surgery, and older age, often coupled with an underlying predisposition to thrombosis, so-called gene/environmental interaction, or the second-hit hypothesis.

Knowledge of VTE risk factors and causes has increased greatly over the last decade. Factor V Leiden in its heterozygous form has been found to be the most common genetic marker of thrombophilia in patients with (VTE). The presence of this marker usually does not change the length of treatment and, if incidentally found in a patient without VTE, does not warrant anticoagulation. The importance of this marker is much greater if the patient has a homozygous defect or a second defect such as prothrombin 20210A, elevated serum homocysteine, anticardiolipin antibodies, lupus anticoagulant, elevation of coagulation factors VIII, IX, or XI, or the relatively rare defects in protein C, protein S, or antithrombin. When combined defects are present, the risk of recurrent VTE may be as high as 70% to 90%. If the patient has a personal or family history of VTE, they may harbor one or more of these defects and selective preoperative screening is important for preoperative planning of procedures. The patient may decline to have such a procedure because the risk of thrombosis is very high, or the surgeon may use the most powerful anticoagulant thrombosis prophylaxis, which may cause slightly more bleeding complications but may be justified in light of the increased thrombotic risk.

We feel that all surgical patients should have appropriate thrombosis risk assessment preoperatively and that the currently established prophylactic modalities be employed, depending on the patient's risk score. Risk of VTE after a surgical procedure is not solely procedure-related but a combination of the procedure being done and the risk of the individual patient. On many occasions, operations that are done on an ambulatory or short-hospital–stay basis may be associated with an extremely high risk and merit longer-term prophylaxis.

The need to decrease the incidence of VTE is now a recognized quality process measure for hospitals and physicians. The National Institutes of Health have also recognized the need to fund venous research and, indeed, two recent requests for funding applications have been released. Most surgeons encounter VTE as a primary complication in patients undergoing major surgery or, more commonly, treating those with postphlebitic syndrome. These problems can be vexing, as few surgical approaches to either acute VTE or venous insufficiency have yielded durable results or widespread adoption. This disease process also affects a younger demographic than does arterial vascular disease, and this drains from an active working demographic.

The good news with VTE is that exciting research is ongoing concerning the basic pathophysiology of how venous thrombi develop and, once formed, how they resolve. This is coupled with the fact that current therapies, both prophylaxis and treatment, are very effective but need to be consistently applied in practice. The current basic pathophysiology of venous thrombosis and thrombus resolution is reviewed by Wakefield and Henke in this issue. It has been known for some time that thrombosis and inflammation are self-amplifying processes. Both anti-inflammatory and proinflammatory experimental strategies have been effective at inhibiting DVT formation or accelerating DVT resolution, depending upon the timing of administration and the age of the thrombus. The role of the cell adhesion molecule family of selectins represents a very promising prophylactic and therapeutic measure that will soon, hopefully, enter human clinical trials.

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Potentially, this therapy could prevent and treat VTE without the downside of anticoagulation. Similarly, the vein wall response to the DVT inflammatory insult is, not surprisingly, complex but seems to follow a typical wound healing course. Thus, the observations put forth confirm that both the thrombus itself is biologically active and resolves in both plasmin and matrix metalloproteinase-dependent manner; but this activation may cause vein wall damage. Interestingly, preliminary experimental observations support early and aggressive thrombus removal to decrease vein wall injury. This certainly has ready translation to current practice.

The standards of care for VTE treatment are unfractionated heparin (UHF) and its derivatives, which include both low-molecular-weight heparin (LMWH) and the pentasaccharides. Dr. Hyers gives a clear and concise review of the types, advantages, and disadvantages of each of these classes of agents. UHF has been the standard initial treatment agent for more than 60 years, is very familiar to physicians and, of course, widely used in vascular surgery. Use of this agent in VTE treatment has a number of disadvantages, including intravenous administration and only a 30% affinity for the clotting proteins, which results in not being able to achieve a therapeutic level in some patients for up to 48 hours or longer. In addition, this agent has an incidence of heparin-induced thrombocytopenia (HIT) 10-fold higher than LMWH and can result in disastrous thrombotic complications.

A great deal of clinical experience in VTE treatment has occurred within the last decade using LMWH preparations. The smaller heparin molecules have a 90% affinity for the clotting proteins, which results in a more predictable dose response. Subcutaneous administration allows for outpatient therapy, and routine coagulation monitoring is not required. The pentasaccharides, including fondaparinux, have not been associated with HIT, and, although relatively new for VTE treatment, may offer certain advantages.

Another area of rapid development is new long-term anticoagulants. The vitamin K antagonist coumadin has been standard of care for several decades, as no other effective oral agents have been available. The downside of vitamin K antagonists is numerous, including the need for constant and continuous patient monitoring, patient variability of response to doses, and the fact that major bleeding occurs in up to 10% of patients. The bottom line is that coumadin can be very dangerous even in the most skilled hands supervising this form of treatment with specialized anticoagulation clinics. There are a great number of drug interactions, food interactions, and other factors that can influence the level of anticoagulation using the vitamin K antagonists. The promise of new drugs that could improve care in patients requiring chronic anticoagulation is an exciting prospect. Dr. Ansell gives a comprehensive overview of new agents that hold particular promise in this regard. Unfortunately, a very large clinical drug development program involving the direct thrombin inhibitor ximelagatran is temporarily on hold pending U.S. Food and Drug Administration concerns regarding hepatotoxicity and possible rebound myocardial infarctions.

The therapy of aggressive thrombus removal for iliofemoral DVT has historically included both surgical thromboembolectomy and use of systemic thrombolysis. The experiences with these techniques have been generally disappointing, primarily because morbidity of the surgical approach is far too high, and bleeding complications related to peripheral thrombolytic agent administration is without significant benefit over intravenous heparin. Peden et al review an exciting approach to aggressive thrombus removal via endovascular techniques. This involves both direct thrombolytic infusion into the thrombus, as well as a catheter-directed thrombus removal. It is the editors' hope that a clinical trial will be done to critically analyze this promising therapy, which could lead to a paradigm change in the treatment of iliofemoral DVT in particular in which the long-term risk of venous insufficiency is highest.

Currently available therapy is very effective for reducing the postphlebitic syndrome beyond standard anticoagulation. However, the adoption of these protocols has been hesitant, in part, because of lack of knowledge. Dr. Partsch reviews strong data supporting early ambulation and compression hose use in patients being treated for DVT. He and his coworkers have been pioneers in the field of compression therapy, including short-stretch bandages, a variety of compression stockings, and other devices to both treat the painful swollen leg and help prevent postthrombotic syndrome. His research has clearly shown that ambulation in certain patients with VTE is safer than bed rest. This article should be of great interest to all those treating VTE and its complications, including postthrombotic syndrome.

A vexing and special DVT problem is effort thrombosis. This disease affects even younger active patients than typical DVT, and can lead to severe upper extremity disability if improperly treated. Active thrombolysis is now well accepted, but the specifics and timing of definitive repair, as well as the use of adjunctive endovascular techniques, is controversial. Drs. Capparelli and Frieshlag provide a good argument for same admission therapy in selected patients.

Endovascular vena caval interruption with the use of inferior vena cava (IVC) filters is now standard, safe, and effective. Whereas a decade ago most filters were placed for either a complication of or a contraindication to anticoagulation, prophylactic use now is most common. This may be, in part, an industry-driven manifestation, as little objective level I evidence exists for use of temporary or optionally retrievable versus permanent filters. Indeed, level I evidence for filter efficacy in general has been scant. Dr. Rutherford gives a comprehensive review of the indications for prophylactic filters and a critique thereof. To complement this, Dr. Rectenwald reviews the data and evidence for use of IVC interruption with standard permanent filters. While some filter types have many years of follow-up, most new filters do not. It is clear to the editors that regardless of the filter type, a conical design makes the most sense for allowing pulmonary embolism trapping and native lysis. It is our hope, as guest editors, that the practicing vascular specialist will be able to glean

readily useful and concise information from these up-to-date and critical reviews.

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