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DEEP VENOUS THROMBOSIS: PREVENTION AND TREATMENT

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Introduction

Venous thromboembolic diseases comprise the spectrum from deep vein thrombosis (DVT) to pulmonary embolism (PE) and have an incidence of approximately 1 per 1,000 annually in adult populations.[1] Rates are slightly higher in men than women. About two-thirds of episodes manifest as DVT and one-third as PE with or without DVT. The major outcomes of venous thrombosis are death, recurrence, post-thrombotic syndrome, and major bleeding due to anticoagulation. Thrombosis is also associated with impaired quality of life, particularly when post-thrombotic syndrome develops.[2] Death occurs within one month of an episode in about 6% of those with DVT and 10% of those with PE.[3] The mortality rate for PE is estimated to be as high as 30% in studies that included autopsy-based PE diagnosis.[4] Mortality rates are lower among patients with idiopathic venous thrombosis and highest among those whose thrombosis occurs in the setting of cancer. Venous thrombosis increases in incidence with age, with a low rate of about 1 per 10,000 annually before the fourth decade of life, rising rapidly after age 45 years and approaching [5-6] per 1000 annually by age 80.5,6 Aging is associated with a steeper rise in incidence of PE as compared to DVT. Morbidity from venous thromboembolic disease appears to be greater in the elderly.[5]

Lower limb: There are more than a quarter-million hospital admissions each year in the United States for acute lower-extremity DVT and PE.[7-9] In hospital patients without prophylaxis, it is estimated that the incidence of isolated calf DVT and proximal DVT is 25% and 7%, respectively.[9, 10] When thrombosis is proximal to the calf, there is a 50% likelihood of pulmonary embolism. There are geographical differences in reports on DVT, with up to twice the reported incidence of calf DVT coming from Europe compared to North America.[10]

Upper limb: Upper-extremity venous thrombosis represents 0.5 to 1.5% of all venous thromboses. The primary form of the disease also is known as “effort thrombosis” or Paget-Schroetter disease. The secondary form of the disease is most commonly a result of central venous catheterization for central venous or cardiac access. Iatrogenic causes of secondary venous thrombosis account for up to 30% of symptomatic subclavian venous thromboses.[11] In addition, studies have shown that clinically silent thrombosis may occur in 20-30% of patients after central venous catheter insertion.[12, 13]

Risk Factors

Multiple studies have consistently identified risk factors for the development of DVT. These risk factors are listed in Table 1. Commonly identified risk factors include age >40 years, prolonged immobility, prior venous thrombotic disease, malignancy, major surgery, obesity, varicose veins, congestive heart failure, myocardial infarction, orthopedic trauma, and estrogen use. An increasing concern during the workup for a DVT is identification of a hypercoagulable disorder (Table 2). Primary disorders involve a specific defect of a hemostatic protein, while secondary disorders result in an indirect effect on the hemostatic pathways.[14-17] All patients with thrombosis at an early age (<45 years), a

Risk Factors for Thromboembolism

Older age	Personal history of previous thrombosis
Male gender	Varicose Veins
Obesity/overweight	Trauma/injury
Immobility	Family member with venous thrombosis
Pregnancy/puerperium	Surgery
Postmenopausal hormone therapy	Type of procedure
Selective estrogen receptor modulating drugs	Hospitalization
Oral contraceptives	Cancer
Long travel	Myeloproliferative disease
Genetic factors affecting coagulation balance	Indwelling foreign body
Antiphospholipid syndrome	

Table 1. Risk factors for developing deep vein thrombosis.

Primary Hypercoaguable States

Genetic Factors Affecting Coagulation Balance

Antiphospholipid syndrome	Protein C deficiency
Factor V Leiden	Protein S deficiency
Factor V Leiden homozygous	Elevated factor V
Prothrombin 20210A	Antithrombin deficiency
Elevated fibrinogen	Elevated factor VIII
Elevated D-dimer	Elevated factor VII
Elevated homocysteine	Elevated factor IX
Heparin cofactor II deficiency	Elevated factor XI
Decreased plasminogen activator inhibitors	dysfibrinogenemia
Increased plasminogen activator inhibitor	

Secondary Hypercoaguable States

Defects of coagulation and fibrinolysis	**Defects of platelets**
Malignancy	Myeloproliferative disorders
Pregnancy	Paroxysmal nocturnal hematuria
Use of oral contraceptives	Diabetes mellitus
Nephrotic syndrome	Hyperlipidemia
Lupus anticoagulant	Cushing's syndromes

Defects of blood vessels and rheology

Immobilization
Postoperative care
Vasculitis
Chronic obliterative arterial disease
Homocysteinemia
Hyperviscosity
Thrombotic thrombocytopenic purpura

Table 2. Primary and secondary hypercoagulable disorders.

Low risk	Uncomplicated minor surgery
	Age ≤40 years
	No risk factors
Moderate risk	Age 40-60 years and no additional risk factors
	Age ≤40 years, major surgery, and no additional risk factors
	Minor surgery with additional risk factors
High risk	Age >60 years and major surgery, with no additional risk factors
	Age 40-60 years and major surgery with additional risk factors, patients with myocardial infarction, and medical patients with risk factors
Highest risk	Age >40 years and major surgery, plus prior thromboembolism, malignancy, or hypercoagulable state
	Major lower-extremity orthopedic surgery
	Hip fracture
	Stroke
	Multiple trauma
	Spinal cord injury

Table 3. Risk Stratification

positive family history of thrombotic disease, thrombosis at an unusual site (mesenteric vein, cerebral vein), or recurrent thromboses without predisposing factors should be screened for hypercoagulability. In considering who needs prophylaxis, patients may be categorized into levels of risk: low, moderate, high, and highest (Table 3). In these categories the incidence of calf vein DVT is 2%, 10-20%, 20-40% and 40-80%, whereas for proximal DVT the incidence is 0.4%, 2-4%, 4-8% and 10-20%, respectively.

Pathogenesis

One or more of three conditions causes thrombi to form in the systemic veins: reduced blood flow in the systemic veins, injury to the vein wall, and the presence of hypercoagulability. These factors remain important in the pathogenesis of pulmonary embolism and are known as "Virchow's Triad."[18, 19]

Lower limb:

Venous stasis is the most important feature predisposing to venous thrombosis. The venous sinuses of the veins are especially vulnerable to stasis and thrombosis. Propagation of the thrombus may then follow upstream or the process may spread retrograde. Thrombi found in veins when blood flow is reduced are composed predominantly of fibrin and entrapped blood cells with relatively few platelets and are often termed red thrombi. The friable ends of these thrombi are the source of the material that eventually becomes pulmonary emboli. Formation of venous thrombi is typically asymptomatic and may involve the superficial or deep venous systems. Deep venous thrombi can propagate into the superficial system.

Upper limb:

Primary axillo-subclavian venous thrombosis is related to chronic venous compression and stenosis in the axillary-subclavian vein at the level of the costoclavicular space. It is seen most commonly in young individuals following vigorous exercise or activity involving hyperabduction of the affected extremity.[20, 21] In the most common form of the disease, the vein is compressed between a hypertrophied scalene tendon and the first rib. Secondary axillo-subclavian venous thrombosis is generally associated with instrumentation of the central venous circulation, direct venous trauma, or the presence of a hypercoagulable disorder. Secondary axillo-subclavian venous thrombosis is an important clinical issue that requires attention. Iatrogenic causes of secondary venous thrombosis account for up to 30% of symptomatic subclavian venous thromboses.[11] In addition, studies have shown that clinically silent thrombosis may occur in 20-30% of patients after central venous catheter insertion.[12, 13] Although it has not been clearly delineated, there are several inciting possibilities for secondary axillosubclavian vein thrombosis; they include endothelial trauma during insertion of the catheter, trauma from the indwelling catheter, venous stasis and fibrin deposition upon the catheter surface, and the effects of infusates on the surrounding vessel. Venous stenosis occurs in 30-40% of patients with central venous catheters.[22, 23]

Natural History

In isolated calf thrombosis, proximal propagation occurs in up to 23% of untreated patients and 10% of patients treated with intravenous heparin. Propagation

to a new segment has been documented in 30% of initially involved limbs and rethrombosis of partially occluded or recanalized segments in 31% of extremities. After completing a course of anticoagulation, the theoretical rate of recurrence is 0.9% per month.[24] Following venous thrombosis, the venous lumen is most often reestablished. Recanalization occurs in an exponential manner over six months.[25] Up to 40% of occluded segments recanalized within seven days while 100% recanalization occurs within 90 days.[26] It appears that venous valvular incompetence occurs after deep venous thrombosis. This is supported by natural history studies that have demonstrated a correlation between segment thrombosis and subsequent valvular incompetence.[27] The development of reflux is highest within the first 6-12 months after development of a DVT.[28] However, up to 30% of segments will develop reflux without evidence of an initial thrombus, and this phenomenon appears to be related to persistent proximal obstruction.[29] The interval between the development of these defects and symptoms and signs of chronic venous insufficiency may range out to 20 years.[30]

The clinical diagnosis of DVT can be unreliable, as the disease mimics the patterns of many other disorders.[18, 31] More than half of the patients who present with the classical symptoms of DVT do not have the disease.[18] Clinical suspicion in combination with diagnostic imaging should be used to confirm the diagnosis.[32] The proportion of patients with clinically suspected DVT, in whom the diagnosis is confirmed by objective testing, increases with the number of risk factors identified. Approximately half of the patients with DVT who develop pulmonary embolism have no symptoms of deep venous disease. This causes a delay in the administration of appropriate prophylactic and therapeutic measures.

Duplex ultrasonography is a popular screening method of choice for the noninvasive assessment of blood flow in leg veins and of valve cusp movement.[33] It also can differentiate between acute and chronic venous thrombosis. All major deep veins of the lower limb can be assessed, but it cannot exclude the presence of thrombi in small veins of the calf. With experience, ultrasonography is accurate, repeatable, and inexpensive.[34] Positive tests indicating above-knee DVT do not require further follow-up unless the condition of the leg significantly worsens. Below-knee DVT requires repeat scanning and is recommended to confirm that there is no antegrade propagation on anticoagulation therapy. Duplex ultrasonography sensitivity and specificity are 94% and 96%, respectively. Overall accuracy is considered to be 95%. Cross-sectional imaging with computed tomography (CT) or magnetic resonance imaging (MRI) is a reliable method of diagnosing venous thrombosis, especially in the pelvic veins.[35] Venography is recommended to validate and diagnose a DVT when duplex ultrasonography has failed to rule out DVT and should be performed prior to iliofemoral thrombolysis or thrombectomy.

A recent review of the evidence strongly supports the use of clinical prediction rules, particularly the Wells model, for establishing the pretest probability of DVT or pulmonary embolism in a patient before ordering more definitive testing.[36] Fifteen studies support the conclusion that when a D-dimer assay is negative and a clinical prediction rule suggests a low probability of DVT or pulmonary embolism, the negative predictive value is high enough to justify foregoing imaging studies in many patients. The evidence in five systematic reviews regarding the use of D-dimer, in isolation, is strong and demonstrates sensitivities of the enzyme-linked immunosorbent assay (ELISA) and quantitative rapid ELISA, pooled across studies, of approximately 95%. Eight systematic reviews found that the sensitivity and specificity of ultrasonography for diagnosis of DVT vary by vein; ultrasonography performs best for diagnosis of symptomatic, proximal vein thrombosis, with pooled sensitivities of 89-96%. The sensitivity of single-detector helical CT for diagnosis of pulmonary embolism varied widely across studies and was below 90% in four of nine studies; more studies are needed to determine the sensitivity of multidetector scanners.[36]

Management

Prevention:

The American College of Chest Physicians (ACCP) has recently provided the following guidelines for DVT prophylaxis.[37] In patients admitted to the hospital with an acute medical illness, major trauma, and spinal cord injury, thromboprophylaxis with a low-molecular-weight heparin (LMWH), low-dose unfractionated heparin (LDUH), or fondaparinux is recommended with grade 1A weighting. For patients undergoing major general, gynecologic, and urological surgery, thromboprophylaxis with LMWH, LDUH, or fondaparinux is recommended. However, for patients undergoing elective hip or knee arthroplasty and hip fracture surgery, an alternative regimen of therapy with a vitamin K antagonist (VKA) with a goal of an international normalized ratio (INR) target of 2.5 (INR range, 2.0 to 3.0) is recommended for 10 to 35 days. All major trauma and all spinal cord injury patients receive thromboprophylaxis. Mechanical methods of thromboprophylaxis are recommended primarily for patients at high bleeding

risk or possibly as an adjunct to anticoagulant thromboprophylaxis.

Lower Extremity DVT:

American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition) on the treatment for venous thromboembolic disease recommend anticoagulant therapy with subcutaneous (SC) LMWH, monitored intravenous, or subcutaneous unfractionated heparin (UFH), unmonitored weight-based SC UFH, or SC fondaparinux followed by VKA.[38] For patients with a high clinical suspicion of DVT, treatment with anticoagulants while awaiting the outcome of diagnostic tests is recommended. In acute DVT, the guidelines recommend initial treatment with LMWH, UFH, or fondaparinux for at least 5 days prior to initiation of VKAs and concomitant administration of LMWH, UFH, or fondaparinux on the first VKA treatment day, and discontinuation of these heparin preparations when the international normalized ratio (INR) is > or = 2.0 for at least 24 hours. For patients with DVT secondary to a transient (reversible) risk factor, three-month treatment with a VKA is recommended. For patients with unprovoked DVT, ACCP recommends treatment with a VKA for at least 3 months followed by an evaluation for the risks to benefits of indefinite VKA therapy. Indefinite anticoagulant therapy is recommended for patients with a first unprovoked proximal DVT or PE and a low risk of bleeding, when this is consistent with the patient's preference, and for most patients with a second unprovoked DVT. The dose of VKA should be adjusted to maintain a target INR of 2.5 for all treatment durations. ACCP recommends at least 3 months of treatment with LMWH for patients with venous thromboembolism (VTE) and cancer, followed by treatment with LMWH or VKA as long as the cancer is active. Treatment with VKA for more than three months is indicated for patients with recurrent VTE or in patients in whom there is a continuing risk factor for VTE. Patients should be followed up for three years to ensure that there is no recurrent thromboembolic event. Discontinuation of anticoagulant therapy in patients with recurrent VTE is associated with an approximate 20% risk of recurrent VTE during the following year and a 5% risk of fatal pulmonary embolism.[39, 40] In patients with a continuing risk factor, which is reversible, long-term therapy should usually be continued until the risk factor is reversed. Anticoagulant therapy should be continued indefinitely in patients with an irreversible risk factor. For prevention of post-thrombotic syndrome (PTS) after proximal DVT, the use of an elastic compression stocking is recommended. For DVT of the upper extremity, we recommend similar treatment as for DVT of the leg. Selected patients with lower-extremity and upper-extremity DVT may be considered for thrombus removal, generally using catheter-based thrombolytic techniques. For extensive superficial vein thrombosis, treatment with prophylactic or intermediate doses of LMWH or intermediate doses of UFH for weeks weeks is recommended.

Upper Extremity DVT:

For patients with acute upper-extremity DVT (UEDVT), treatment is as described for lower-extremity DVT including treatment with a VKA for more than three months. If the DVT is due to a central venous catheter and the catheter is removed, then the duration of anticoagulation can be reduced to three months. Except in unusual circumstances, routine use of catheter-directed thrombolytic therapy is not recommended.

Decompression of Thoracic Outlet:

Acute upper-extremity DVT can be due to thoracic outlet syndrome. The frequency of PTS after UEDVT ranges from 7-46% (weighted mean 15%). Residual thrombosis and axillosubclavian vein thrombosis appear to be associated with an increased risk of PTS, whereas catheter-associated UEDVT may be associated with a decreased risk. There is currently no validated, standardized scale to assess upper-extremity PTS and little consensus regarding the optimal management of this condition. Quality of life is impaired in patients with upper-extremity PTS, especially after DVT of the dominant arm.[41] These patients often present with obstructive symptoms, and if acute thrombosis is noted, common practice is to perform catheter-directed thrombolysis followed by resection of the first rib.[42] Decompression of the thoracic outlet requires resection of either the clavicle and/or the first rib with division of the scalene muscle fibers at their insertion; division of the subclavius tendon and local venolysis must supplement each of these procedures.[43] First rib resection has most commonly been accomplished from a transaxillary approach but may be performed by supraclavicular, transclavicular, and infraclavicular approaches.[41] If venous repair is considered a possibility, then either supraclavicular, anterior clavicular, or infraclavicular approaches are required.

Pulmonary Embolism:

For patients with a high clinical suspicion of pulmonary embolism (PE), treatment with anticoagulants while awaiting the outcome of diagnostic tests is recommended. Patients with confirmed PE who are hemodynamically compromised should be considered for a short-course thrombolytic therapy.[38] For those with nonmassive PE, the use of thrombolytic therapy should

also be considered. In acute PE, initial treatment with LMWH, UFH, or fondaparinux for at least five days is recommended, with subsequent initiation of vitamin K antagonists together with LMWH, UFH, or fondaparinux on the first treatment day and discontinuation of these heparin preparations when the INR is > or = 2.0 for at least 24 hours. For patients with PE secondary to a transient (reversible) risk factor, therapy with a VKA should continue for three months. For patients with an unprovoked PE, it is recommended that therapy with a VKA should continue for at least three months and that all patients be evaluated for the risks to benefits of indefinite therapy. The dose of VKA should be adjusted to maintain a target INR of 2.5 (INR range, 2.0 to 3.0) for all treatment durations.

Thrombolysis:

Percutaneous clot removal using thrombolysis, mechanical thrombectomy, or a combination of the two is fast becoming a treatment of choice for patients presenting with acute iliofemoral and axillosubclavian deep vein thrombosis.[42, 44] By restoring venous patency and preserving valvular function, catheter-directed thrombolytic therapy potentially affords an improved long-term outcome in selected patients with DVT. In selected patients with extensive acute proximal DVT (i.e., iliofemoral DVT, symptoms for <14 days, good functional status, life expectancy of >1 year) who have a low risk of bleeding, catheter-directed pharmacomechanical thrombolysis is suggested by ACCP.[38] This percutaneous therapy should include correction of any underlying venous lesions.

Conclusion

Management of DVT has progressed significantly in the last decade with the recognition of the need for aggressive DVT prophylaxis, improvements in diagnosis, and the use of more aggressive standards on initial and chronic therapy.

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