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Venous Thromboembolism

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Venous thromboembolism causes substantial disability and death. The incidence of deep venous thrombosis (DVT) is about 1 per 1000 person years. The most serious and potentially preventable complication, pulmonary embolus, kills an estimated 50,000 Americans each year.[1] Venous stasis secondary to chronic valvular incompetence, often a consequence of venous thrombosis, causes varying degrees of pain, edema, and ulceration. The changing demographic patterns, particularly the aging of society, are increasing the risk of venous thromboembolism and the importance of prevention. Recent identification of inherited defects causing thrombosis (inherited thrombophilias) allows improved prevention through identification of individuals at high risk. The knowledge and tools for effective prevention and treatment are available but currently underused.[2] Early identification, office-based diagnostic tests, safer treatments, and targeted education programs for physicians may offer the chance to reduce the incidence of venous thromboembolism and associated morbidity.

Pathophysiology

Virchow hypothesized three factors that predispose a person to venous thrombosis: a hypercoagulable state, injury to the vascular intima, and venous stasis. A century of research has verified this hypothesis. DVT is now understood to be a multifactorial disorder, involving a combination of genetic risk factors and acquired condi-

tions.[3] Known genetic causes are present in 25% of unselected DVT cases and 63% of familial cases.[4] This percentage will probably increase as research identifies more genetic causes. Some conditions that predispose to thrombosis have both genetic and acquired components. Examples are elevated levels of factor VIII[5] and high plasma homocysteine levels. Stasis is the most common precipitating factor. Vascular injury is often the result of surgery or trauma.

A hypercoagulable state results from a disruption of the normal balance between the procoagulant system and the anticoagulant system. The natural anticoagulant system works to confine a beneficial thrombosis to the site of injury and prevent propagation. Major components of this system include antithrombin III, protein C, and protein S. Protein C is activated to the enzyme APC, which functions as a natural anticoagulant by inactivating procoagulant factors Va and VIIIa in the presence of protein S. Antithrombin III directly inhibits thrombin.

Modern molecular genetics is rapidly elucidating the prothrombotic mutations that contribute to hypercoagulable states. The anticoagulant system is impaired by the factor V Leiden mutation, and by deficiencies of proteins C and S and antithrombin. Raised plasma levels of prothrombin 20210A and factor VIII increase risk by accelerating the procoagulant system.

Epidemiology

Reliable incidence data for DVT are not available. Autopsy series show that DVT is often present when not clinically suspected, so hospital discharge diagnosis and death certificate data underestimate the true prevalence. Declining autopsy rates in the United States compound the problem. The best incidence data are from Malmö General Hospital in Sweden, which has maintained an autopsy rate greater than 75% since 1957. The incidence of DVT and fatal pulmonary embolism has been remarkably stable at 35%, representing 9% of all hospital deaths.[6] The Worcester DVT study, a regional survey of hospital discharge diagnoses, reported a diagnosis of DVT in 0.9% of all hospital discharges. The incidence rate increased exponentially with age, rising by a factor of approximately 200 between ages 20 and 80 years.[7] Studies using screening techniques to evaluate hospitalized patients identified surgery of the pelvis or lower extremity and anesthesia lasting more than 30 minutes as the highest risk events (see Chapter 1). More patients hospitalized for medical reasons experience an episode of DVT than did surgical patients because of the greater number of total admissions.

Table 7.1. **Prevalence of Risk Factors for Thrombosis**

Factor	General population[a]	Patients with thrombosis (%)
Genetic		
Factor V Leiden mutation (APC resistance)	~1 in 20	~20[b]
Prothrombin 20210A	~1 in 50	~6
Protein C deficiency	~1 in 300	~3
Protein S deficiency	~1 in 300	~1–2
Antithrombin deficiency	~1 in 3000	~1
Mixed (genetic and acquired components)		
High concentration factor VIII	1 in 10	25
Hyperhomocystinemia	1 in 20	10

[a]Varies significantly in different ethnic populations.

[b]Up to 60% in pregnant patients with deep venous thrombosis (DVT).

Table 7.1 lists the prevalence of risk factors for venous thrombosis.[3] The most common inherited thrombophilia is APC resistance caused by a point mutation producing an abnormal protein known as factor V Leiden. It is present in 5% of Caucasian Americans but has a much lower prevalence in other ethnic groups.[8,9] Women with the factor V Leiden mutation are at increased risk for DVT when taking oral contraceptives. The lifetime risk for DVT in factor V Leiden heterozygotes is approximately 10% and for homozygotes is >80%. Direct molecular genetic testing for the R506Q mutation in the factor V gene is available. Genetic testing can distinguish homozygotes and is the definitive test. The American College of Medical Genetics recommendations for who should be tested for factor V Leiden are listed in Table 7.2.[10] General population screening is not recommended.

Table 7.2. **American College of Medical Genetics (ACMG) Guidelines for Factor V Leiden Testing**

Testing is recommended for individuals who have:
Any venous thrombosis and are <50 years of age
Venous thrombosis in unusual sites
Recurrent venous thrombosis at any age
Venous thrombosis and a strong family history of thrombotic disease
Venous thrombosis during pregnancy or in women taking oral contraceptives
Relatives with venous thrombosis who are under age 50

Clinical Approach

A logical set of principles are basic to the structure of the clinical approach:

1. Venous thrombosis is common. Thrombosis results when an individual with an inherited predisposition to thrombosis suffers venous stasis or vascular injury. Testing to identify the causes of thrombophilia is important.
2. The location of the thrombus is important. The primary source (90%) of pulmonary emboli is the deep veins of the proximal lower extremities. Thrombi limited to the calf pose limited risk (<5%) of pulmonary embolism, but extension to proximal veins occurs.[11] This point is critical to the diagnostic approach outlined in this chapter.
3. Pulmonary embolism is not an independent disease but a complication of DVT. Pulmonary embolism is discussed in Chapter 86.
4. Pulmonary embolism kills quickly; 75% to 90% of those affected die within the first few hours. With limited opportunity for effective diagnosis and treatment, identification of high-risk individuals and primary prevention of DVT is the goal.

Prevention

The key to prevention of thromboembolism is physician recognition of patients at risk, vigorous use of effective treatment, and prophylactic regimens. Selection of appropriate treatments to prevent DVT is imperative whenever a hypercoagulable state is identified or when venous stasis or vascular injury is likely. The 1986 National Institutes of Health (NIH) Consensus Conference outlined such a strategy, and it has been updated.[12] Prophylactic regimens to prevent DVT are discussed in Chapter 57.

Clinical Risk Stratification

Evaluation of the patient with suspected DVT begins with a thorough history and physical examination. DVT occurs predominantly in patients with clinical risk factors. The limitations of physical examination to identify DVT are well known, but physical findings are useful when present. Table 7.3[13,16] lists clinical risk factors and findings that are associated with DVT. Formal clinical risk scoring systems

Table 7.3. **Clinical Risk Factors and Physical Findings Associated with Deep Venous Thrombosis (DVT)**

Risk factors	Physical findings
Active malignancy	Localized tenderness along distribution of deep veins
Recently bedridden	Unilateral pitting edema
Recent paralysis/paresis	Thigh or calf swelling >3 cm compared to the asymptomatic limb
Recent limb immobilization	Dilated superficial (nonvaricose) veins in symptomatic limb only
Trauma	Erythema in symptomatic limb only
Hospital or nursing home confinement	
Pregnancy/puerperium	
Strong family history of DVT	

have been developed to stratify patients with suspected first DVT into low, moderate and high-risk groups. Risk stratification then helps guide evaluation as described below, especially the need for follow-up evaluation if initial studies are negative.[13–16]

Diagnostic Tests

D-Dimer Assay

D-dimer, a degradation product of cross-linked fibrin, is released into the blood during fibrinolysis. D-dimer testing is highly sensitive, but has poor specificity in the diagnosis of DVT because many conditions can lead to elevated serum D-dimer levels.[17] It has been studied as an adjunctive test to help rule out DVT. There are several types of D-dimer assays currently available for clinical use, including enzyme-linked immunosorbent assay (ELISA), latex agglutination, and whole blood agglutination. ELISA testing is very accurate, but the conventional test takes at least several hours and may not be practical for clinical use. Several rapid ELISAs that can be run in less than an hour are now available and have sensitivity that is roughly equivalent to standard ELISA.[18] Latex agglutination assays are inexpensive and rapid, but lack sufficient sensitivity to be useful as screening tests.[19] Whole blood agglutination assays have several advantages. They require only a drop of blood, rather than plasma, and provide results in as little as 2 minutes. Their sensitivity is reported to be similar to that of ELISA.[20] Two studies suggest that DVT can

be reliably ruled out in low-risk patients using formal risk stratification in whom whole blood agglutination assay D-dimer testing is negative.[15,16]

Ultrasonography/Duplex Scanning

Real-time compression ultrasonography has been demonstrated to be a reliable technique for noninvasive evaluation of proximal venous thrombosis.[21,22] With this technique the veins under evaluation are visualized and the ability to compress the vein with probe pressure measured. The technique is accurate for thrombi above the knee, with sensitivity and specificity reported to be more than 90% in most series. It is less useful for diagnosing thrombi below the knee. Real-time ultrasonography is widely available, but the reliability of the results may vary with the expertise of the technologist performing the study. Duplex scanning combines real-time ultrasonography with a pulsed Doppler study to diagnose DVT.[23] The reported sensitivity and specificity of this test ranges from 85% to 95%. It also is of limited value for diagnosing calf thrombi.

Duplex scanning should not be confused with a Doppler study. Doppler evaluation of the lower extremity requires only a small handheld unit and does not use B-mode ultrasonography. It detects only venous occlusion, so significant mural thrombi may be missed. The test has poor sensitivity and no role as a definitive diagnostic test.

Contrast Venography

Contrast venography has long been considered the standard by which all other diagnostic tests for DVT are measured. Performed according to defined techniques, it is highly accurate and has the advantage of reliably diagnosing thrombosis below the knee.[24] Risks include phlebitis, contrast allergy, local extravasation of dye, and discomfort. The overall complication rate is 4%, and the risk of major complications due to a contrast reaction is 1%. Its main use currently is in the evaluation of high-risk patients with a negative compression ultrasound or for diagnosis of recurrent DVT.

Other Diagnostic Tests

Impedance plethysmography and radiofibrinogen scanning are other tests that have been used in the past for diagnosis of DVT. Because of the wide availability of compression ultrasonography, these tests are now rarely used.

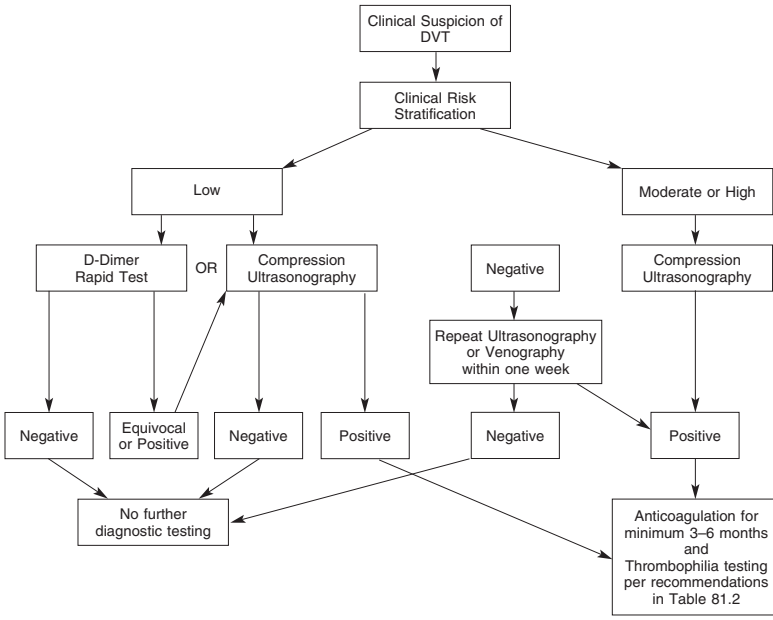

Fig. 7.1. Diagnostic approach to the patient with suspected lower extremity deep venous thrombosis (DVT).

Diagnostic Approach

Many diagnostic strategies for the evaluation of DVT have been proposed,[25] and the preferred strategy will likely change over time. Based on current data we propose the diagnostic approach outlined in Figure 7.1. Using this approach, the evaluation of the patient with suspected DVT should begin with clinical risk stratification. Existing formal scoring systems that allow rapid stratification of patients as low, moderate, or high risk have been clinically validated.[13,16] Moderate- and high-risk patients should promptly undergo compression ultrasound or duplex scanning. A negative study in these patients should be followed by either venography or repeat ultrasound within 1 week. Patients with low clinical risk may undergo D-dimer testing or immediate ultrasound. If D-dimer or ultrasound is negative, then further evaluation is not required. Patients with a positive D-dimer should have ultrasound. Patients with a positive ultrasound or venogram should be treated with anticoagulation.

Treatment

The diagnosis of proximal DVT requires prompt institution of anticoagulation with heparin or low molecular weight heparin. The traditional approach is intravenous administration of unfractionated heparin. Standard heparin is a heterogeneous mixture of polysaccharide chains ranging in molecular weight from about 3,000 to 30,000. It acts by binding to plasma antithrombin III and inactivating thrombin and factor Xa. These enzymes are protected by fibrin, so higher doses are required to stop extension of a thrombus than to prevent its initial formation. Heparin does not directly prevent embolism or promote thrombus dissolution.

Heparin therapy is usually administered intravenously with an initial 80 U/kg bolus followed by continuous infusion of 18 U/kg/h.[26] The goal of therapy is to maintain the partial thromboplastin time (PTT) at 1.5 to 2.0 times the control value. Optimal timing of PTT measurements has yet to be firmly established. The American College of Chest Physicians (ACCP) recommends treating with heparin for 4 to 5 days, until warfarin therapy increases the international normalized ratio (INR) to the 2.0 to 3.0 range. The INR is a worldwide system used to standardize prothrombin times among laboratories.

The major complications of heparin therapy include hemorrhage, thrombocytopenia, osteoporosis, and anaphylaxis. The risk of hemorrhage increases with age, significant coexistent illness, and the presence of known bleeding sites. Platelet count should be checked daily to monitor for thrombocytopenia during heparin therapy. The effects of heparin can be terminated by intravenous injection of protamine sulfate.

Low molecular weight heparins (LMWHs) are fragments of standard heparin with mean molecular weights of 4000 to 6000. There are three LMWHs available in the United States: dalteparin, enoxaparin, and tinzaparin. LMWHs are theoretically superior to unfractionated heparin because of greater anticoagulant specificity (primary action on factor Xa), a more predictable anticoagulant response, fewer complications, and a longer plasma half-life.[27] Many studies have evaluated specific LMWHs for the treatment of DVT, and a meta-analysis concluded that LMWHs administered subcutaneously in fixed doses, adjusted for body weight, and without laboratory monitoring are more effective and safer than adjusted-dose standard heparin.[28] A Cochrane Database systematic review found LMWH to be at least as effective as heparin in preventing recurrent thromboembolism with lower risk of hemorrhage and lower overall mortality.[29] Although LMWHs are more expensive on a per-unit basis, they may

lower the total cost of treatment per episode of DVT. LMWH should be continued for 4 to 5 days until the patient is therapeutic on warfarin with an INR of 2.0 to 3.0.[26]

Two studies have compared the safety and efficacy of subcutaneous LMWH administered at home with intravenous heparin in the hospital.[30,31] These studies demonstrated equivalent safety and efficacy. However, 30% to 60% of potentially eligible patients were excluded from the studies because of additional risk factors. A more recent study compared treatment of DVT with LMWH in hospital for 10 days vs. starting therapy at home.[32] There was no significant difference in outcome between the two groups; however, total costs for the home treatment group were 56% less than the costs for the hospital treatment group. Home-based treatment of DVT with LMWH is becoming more common. Effective protocols for home therapy with LMWH involve a multidisciplinary approach including the physician, pharmacy, and home health nurse. Contraindications to home treatment are listed in Table 7.4.[33]

After treatment with heparin or LMWH, anticoagulation is continued with warfarin. Warfarin should be started concurrently with heparin or LMWH. The duration of warfarin therapy is controversial.[34] The ACCP guideline gives the following recommendations regarding duration of anticoagulation: 3 to 6 months for DVT associated with transient known risk (e.g., surgery), >6 months for idiopathic DVT, and lifelong therapy for recurrent DVT or if associated with a persistent risk factor.[26] The dosage of warfarin is adjusted to maintain a prothrombin time approximately 1.5 times control or an INR of 2.0 to 3.0.[26]

Anticoagulation therapy carries substantial risk of hemorrhage. Warfarin has a narrow therapeutic ratio and is a major cause of pre-

Table 7.4. **Relative and Absolute Contraindications to Home Treatment of DVT**

Concurrent pulmonary embolism
Active bleeding or high clinical risk for bleeding
Familial bleeding disorder
Thrombocytopenia
Severe liver disease
Hemodynamic instability
Limited cardiopulmonary reserve
Significant renal insufficiency
Pregnancy
Severe leg pain and swelling
Uncertain compliance or follow-up

ventable adverse drug reactions. Current recommendations suggest daily measurement of the prothrombin time during initiation of warfarin therapy. Once the INR is in the therapeutic range for two consecutive measurements, weekly monitoring is acceptable. The measurement interval can be extended to 2 to 4 weeks for patients on long-term anticoagulation with stable prothrombin times.[26,33] Optimal management of anticoagulation therapy requires a coordinated program of patient education, drug–drug and drug–food interaction detection, systematic adjustment of warfarin dosage based on prothrombin times, fail-safe systems to communicate the recommendations to patients, and implementation of a patient registry. Organized anticoagulation clinics are cost-effective and demonstrate superior outcomes.[35]

Thrombolytic therapy for DVT has been investigated because it theoretically could prevent postphlebitic syndrome by lysing the clot. It may be appropriate for selected patients with massive iliofemoral DVT. Unfortunately, studies of this therapy have shown a significant increase in major hemorrhage and it is not generally recommended for uncomplicated DVT.[33,36]

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