

Superficial thrombophlebitis or deep vein thrombosis?

Superficial thrombophlebitis (phlebitis) and deep vein thrombosis (DVT) are both common conditions and they share some clinical features and risk factors. It is important to differentiate between the two disorders because they are managed differently. In part one of this two-part article, the clinical features and the differential diagnosis of phlebitis and DVT are examined. Part two will examine the management options for each condition.

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Superficial thrombophlebitis is a common inflammatory-thrombotic process that may occur spontaneously or as a complication of medical or surgical interventions. It has the same pathophysiology and pathogenesis as deep vein thrombosis (DVT) and shares most of its risk factors.

Although uncommon, a superficial thrombophlebitis can sometimes progress through perforating veins to adjacent deep veins. Therefore, not surprisingly, the incidence of associated DVT and pulmonary embolism (PE) in people with superficial thrombophlebitis is relatively high.¹

However, ruling out a DVT in this clinical setting is difficult and often further testing is required to evaluate for a DVT. No single physical finding or combination of symptoms and signs is sufficiently accurate to establish the diagnosis.

Epidemiology

Superficial thrombophlebitis is so common that it is difficult

to obtain valid estimates of its frequency. The exact incidence of DVT is also unknown because most studies are limited by the inherent inaccuracy of the clinical diagnosis of peripheral venous disorders. More importantly, most DVTs are occult and usually resolve spontaneously without complication; therefore, some DVTs are never diagnosed.

The existing data probably underestimate the true incidence of DVT, but the incidence of venous thrombosis (including DVT) in hospitalised patients is considerably higher and varies from 20 to 70%.²

Age is not an independent risk factor for superficial thrombophlebitis, but the incidence of other recognised risk factors increases with age. This leads to an overall increased risk with increasing age.¹

The overall incidence of venous thromboembolic diseases is increasing as the population ages. It rises markedly in persons 60 years and older, and may be as high as 900 cases per 100,000 by the age of 85 years.³ DVT usually

affects individuals older than 40 years and the male-to-female ratio is 1.2:1, indicating that males have a higher risk of DVT than females.^{2,3}

Pathophysiology

Microscopic thrombosis is a normal part of the dynamic balance of haemostasis. In 1846, the German pathologist Virchow recognised that if this dynamic balance was altered by venous stasis, abnormal coagulability, or vessel wall injuries, microthrombi could propagate to form macroscopic thrombi. In the absence of a triggering event, neither venous stasis nor abnormal coagulability alone causes clinically important thrombosis, but vascular endothelial injury does reliably cause thrombus formation. The initiating injury triggers an inflammatory response that results in immediate platelet adhesion at the site of injury. Further platelet aggregation is mediated by thromboxane A₂ and by thrombin.

Platelet aggregation due to thromboxane A₂ is inhibited reversibly by non-steroidal anti-inflammatory drugs (NSAIDs) and irreversibly by aspirin, but these drugs do not affect thrombin-mediated platelet aggregation. Therefore, for this reason, neither treatment is very effective for preventing or treating venous thrombosis.

The formation, propagation, and dissolution of venous thrombi represent a balance between thrombogenesis and the body's protective mechanisms (specifically, the circulating inhibitors of coagulation and the fibrinolytic system). The development of venous thrombosis is best understood as the activation of coagulation in areas of reduced blood flow, which explains why the most successful prophylactic regimens are anticoagulation and minimisation of venous stasis.

DVT

DVT of the lower extremity usually begins in the deep veins of the calf around the valve cusps or within the soleal plexus. A minority of cases arise primarily in the iliofemoral system as a result of direct vessel wall injury, such as from hip surgery or intravenous catheters. The vast majority of calf vein thrombi dissolve completely without therapy and approximately 20% propagate proximally, which usually occurs before embolisation.² The process of adherence and organisation of a venous thrombus does not begin until 5-10 days after thrombus formation. Until this process has been established fully, the non-adherent disorganised thrombus may propagate and/or embolise.

However, not all venous thrombi pose equal embolic risk and isolated calf vein thrombi carry a limited risk of PE.²

Aetiology

Risk factors for superficial thrombophlebitis include a history of local trauma, prior similar episodes, varicose veins (veins that have become enlarged and tortuous without phlebitis), prolonged travel, hormone use, tobacco use or family history of blood coagulopathies. However, the absence of identifiable risk factors has no prognostic value. The most important clinically identifiable risk factors are a prior history of superficial thrombophlebitis and/or DVT.

The risk of DVT in a patient with superficial thrombophlebitis is remote. One case-series study found that it occurred very occasionally if the thrombophlebitis extended above the knee.⁴

The clinical evaluation of patients with suspected DVT is via an assessment of risk factors. Specific risk factors for venous thromboembolic disease (mainly DVT and/or pulmonary embolism; PE) include increasing age, prolonged immobility, surgery, trauma, malignancy, pregnancy, oestrogenic medications and hormone therapy, congestive heart failure, hyperhomocysteinemia, and diseases that alter blood viscosity (eg, polycythemia, sickle-cell disease, and multiple myeloma), and inherited thrombophilias. At least one established risk factor is present in approximately 75% of patients who develop

venous thromboembolic disease, and up to 30% of patients with DVT or PE may have a thrombophilia.^{5,6} Evaluation for thrombophilias should be considered in patients younger than 55 years with an idiopathic episode of DVT, patients with recurrent thrombosis, and patients with a family history of thromboembolism.³ The diagnosis of DVT is confirmed in only 20-30% of emergency admissions with clinically suspected DVT, and a clinical study evaluating 1102 acutely ill, immobilised admitted general medical patients, found four factors to be independently associated with an increased risk for venous thromboembolism (VTE): presence of an acute infectious disease, age >75 years, cancer, and history of prior VTE. Most of these factors were asymptomatic and diagnosed by venography of both lower extremities.⁷

Clinical features

Patients with superficial thrombophlebitis often describe a history of a gradual onset of localised tenderness, followed by the appearance of an area of erythema along the path of a superficial vein. Patients may also complain of a hard, painful "knot" in a previous varicose vein.

The classic signs of DVT, including Homans' sign (pain on passive dorsiflexion of the foot), oedema, tenderness, and warmth, are difficult to ignore, but they are of low predictive value and can occur in other conditions such as musculoskeletal injury, cellulitis, and venous insufficiency.⁶ Many DVT patients are asymptomatic;

Box : Clinical features of DVT and thrombophlebitis

Superficial thrombophlebitis	DVT
<p><i>Inspection</i></p> <p>Erythema, oedema, and pain are common</p> <p>Swelling may result from acute venous obstruction (as in DVT) or venous reflux</p> <p>Normal veins are distended visibly at the foot, ankle, and occasionally in the popliteal fossa</p> <p><i>Palpation</i></p> <p>Superficial thrombophlebitis is characterised by the finding of a palpable, indurated, cordlike, tender, subcutaneous venous segment</p> <p>Palpation of a painful or tender area may reveal a firm, thickened, thrombosed vein</p> <p>Palpable thrombosed vessels are virtually always superficial</p>	<p><i>Inspection</i></p> <p>Oedema is principally unilateral</p> <p>Erythema and local pain may occur</p> <p>Venous distension and prominence of the subcutaneous veins</p> <p><i>Palpation</i></p> <p>Tenderness, if present, is usually confined to the calf muscles or along the course of the deep veins in the medial thigh</p> <p>Homans' sign: discomfort in the calf muscles on forced dorsiflexion of the foot with the knee straight and it is neither sensitive nor specific: it is present in less than 1/3 of DVT patients, but is found in more than 50% of patients without DVT</p>

however, the history may include: unilateral oedema, non-specific leg pain in about 50% and tenderness in 75%, which could also be found in 50% of patients without objectively confirmed DVT.⁶

The pain and tenderness associated with DVT does not usually correlate with the size, location, or extent of the thrombus. But, the signs and symptoms of DVT are related to the degree of obstruction to venous outflow and inflammation of the vessel wall. Darkened, discoloured, stained skin or non-healing ulcers are typical signs of chronic venous stasis, particularly along the medial ankle and the medial lower leg. Chronic varicosities or telangiectasias also may be observed and bedside manoeuvre, such as the Perthes percussive test, can help to assess if venous segments are interconnected.⁸ During

this test, the propagation of a palpable pulse wave suggests that a fluid-filled vessel with open or incompetent valves connects the two locations.

Differential diagnosis

Superficial thrombophlebitis should be differentiated from DVT, Table 1. Others conditions to be differentiated may include Baker's cyst, postphlebitic syndrome with or without chronic venous insufficiency, and lymphoedema. It is also often confused with cellulitis.

Although the risk of DVT in patients with superficial thrombophlebitis is remote, those with superficial thrombophlebitis extending to the saphenofemoral junction are at higher risk for associated DVT.⁴ In one case-series, about 40% of patients with superficial thrombophlebitis,

without coexisting varicose veins and with no other obvious aetiology (eg, intravenous catheters, intravenous drug abuse, and soft tissue injury) had an associated DVT.⁴

The value of various diagnostic tests and imaging studies in predicting the presence of DVT depends on the likelihood of disease in each risk group.⁶ A well-validated clinical prediction rule can be used for risk stratification of patients with suspected DVT. For example, The Wells clinical prediction guide enables physicians to reliably stratify their patients into high-, moderate-, or low-risk of DVT.⁹ It incorporates risk factors, clinical signs, and the presence or absence of alternative diagnoses.

Used in combination with D-dimer or Doppler ultrasound tests, a prediction rule can reduce the need for contrast venography, as well as the likelihood of false-

positive or false-negative test results.⁶

Blood tests rarely are helpful in the diagnosis of superficial thrombophlebitis, except in those patients at risk for an underlying hypercoagulable state. D-dimer is a unique degradation product produced by plasmin-mediated proteolysis of cross-linked fibrin that is often measured in the evaluation for DVT and PE. It has an important role in the diagnosing DVT,^{10,11} but its value in detecting superficial thrombophlebitis is of little clinical use.¹²

D-dimer testing

D-dimer fibrin fragments are present in fresh fibrin clot and in fibrin degradation products of cross-linked fibrin. Monoclonal antibodies specific for the D-dimer fragment are used to differentiate fibrin-specific clot from non-cross-linked fibrin and from fibrinogen. These specific attributes of the D-dimer antibodies account for their high sensitivity for venous thromboembolism.¹³ However, D-dimer level may be elevated in any medical condition where clots form, such as in trauma, recent surgery, haemorrhage, cancer, and sepsis. Many of these conditions are associated with higher risk for DVT.

D-dimer is sensitive for proximal vein DVT but less so for calf vein DVT. A large study, in low-risk patients with low pretest probability for DVT, confirmed that a negative SimpliRED (A rapid qualitative RBC agglutination assay) D-dimer result rules out DVT and ultrasonography was not required in these patients.¹⁴ In addition,

D-dimer levels only remain elevated in DVT for about seven days and patients presenting later than that in the course, after clot organisation and adherence have occurred, may have low levels of D-dimer. Therefore, the D-dimer test should be used to rule out DVT rather than confirm it.

Many different D-dimer assays are available, with varying sensitivities and specificities, and physicians should know their hospital's D-dimer assay. Most studies have confirmed the clinical utility of D-dimer testing, and most clinical algorithms incorporate their use.

The laboratory based enzyme linked immunosorbent assay (ELISA) is currently advocated in the literature as the best D-dimer test for excluding VTE in a hospital setting. Stein et al reported that ELISA for D-dimer has an overall sensitivity of 96% for DVT and 95% for PE.¹⁵ A recent meta-analysis showed that the qualitative assays (SimpliRED D-dimer and Clearview Simplify D-dimer) have a lower sensitivity (that is, a higher number of false negatives) but higher specificity (that is, a lower number of false positives) than the quantitative assays (Cardiac D-dimer and Triage D-dimer). The latter seem, therefore, better suited to rule out DVT in suspected patients as they decrease the pre-test probability of VTE more effectively.¹³ The same meta-analysis concluded that the quantitative D-dimer tests (Cardiac D-dimer and Triage D-dimer) have similar sensitivity to ELISA for D-dimer.

Other laboratory tests

Several common hypercoagulable states can be identified through

laboratory studies. Some of these states include resistance to activated protein C (most often due to factor V Leiden), protein C deficiency, protein S deficiency, antithrombin III deficiency, antiphospholipid antibodies and/or prothrombin gene 2010-a mutation (factor II mutation). These are rare causes of DVT and are primarily indicated when DVT is diagnosed in patients younger than 50 years, when there is a confirmed family history of a hypercoagulable state or a familial deficiency, when venous thrombosis is detected in unusual sites, and in the clinical setting of warfarin-induced skin necrosis.

The prothrombin time (PT) and activated partial thromboplastin time (aPTT) are not useful in the diagnostic evaluation of patients with suspected superficial thrombophlebitis or DVT, and most patients have a normal PT and aPTT. Mahmoodi et al found that microalbuminuria was independently associated with an increased risk for VTE and the risk of VTE rose in tandem with the rate of urinary albumin excretion.¹⁶ The annual incidence of VTE was 0.12% among participants with <15 mg albumin per 24-hour urine collection compared with 0.40% among those with 30–300 mg albumin per 24 hours. Adjusted hazard ratio for microalbuminuria versus normoalbuminuria (ie, <30 mg/24 h) was 2 (P < 0.001).

Imaging studies

Proper diagnosis of venous system disease often requires both functional and anatomic information about the venous circulation. Diagnosing DVT and

committing patients to the risks of anticoagulation therapy without confirmatory objective testing is unacceptable.

The standard procedure for evaluating patients with suspected DVT has been contrast venography. Nowadays, non-invasive studies have essentially replaced venography as the initial diagnostic test of choice. The reasons for that include allergic reactions to contrast material, contrast-induced DVT, technical difficulties, inadequate studies, inter-observer variability, and lack of availability. Contrast venography is either contraindicated or non-diagnostic in as many as 20–25% of patients, and compression ultrasonography is considered the most appropriate study in suspected lower extremity DVT.¹¹ Controversy still exists over the use of noninvasive studies such as duplex ultrasonography for the diagnosis of suspected calf vein DVT, as it is relatively insensitive for calf vein thrombosis.¹¹ In ambulatory outpatients with suspected DVT, the sensitivity of duplex ultrasonography for proximal vein thrombosis is 97%, and it remains the initial diagnostic test of choice. CT venography is the best diagnostic modality for suspected iliofemoral DVT. All patients with superficial thrombophlebitis above the knee should undergo duplex ultrasonography as the initial diagnostic modality of choice to rule out DVT. For patients with superficial thrombophlebitis below the knee, duplex ultrasonography is only indicated for signs and symptoms consistent with a DVT (eg, asymmetrical swelling, erythema, and pain).

Superficial thrombophlebitis in lower extremity varicose veins has an extremely low incidence of DVT.¹⁷

Compression ultrasonography

Technological advances in ultrasonography have permitted the combination of real-time ultrasonographic imaging with Doppler flow studies (duplex ultrasonography). The major ultrasonographic criterion for detecting venous thrombosis is failure to compress the vascular lumen, presumably because of the presence of occluding thrombus. The absence of the normal phasic Doppler signals arising from the changes to venous flow provides indirect evidence of venous occlusion.

Duplex ultrasonography is also helpful to differentiate venous thrombosis from haematoma, Baker's cyst, abscess, and other causes of leg pain and oedema. Ultrasound assessment has several limitations: its accuracy depends on the operator; it cannot distinguish between an old clot and a new clot; and it is not accurate in detecting DVT in the pelvis or the small vessels of the calf, or in detecting DVT in the presence of obesity or significant oedema. Causes of false-positive examinations include superficial thrombophlebitis, popliteal cysts, and abscess.⁶ In addition, venous thrombi proximal to the inguinal ligament are difficult to visualise and non-occluding thrombi may be difficult to detect. Many studies have confirmed the diagnostic sensitivity and specificity of duplex ultrasonography for proximal vein thrombosis. Sensitivity of duplex ultrasonography for proximal vein DVT is 97% but only 73% for calf

vein DVT).^{11,13}

The negative predictive value (NPV) for proximal vein DVT is 99% and overall specificity is 95%. The incidence of VTE following normal imaging tests, such as compression ultrasonography in patients suspected of DVT, is around 1–2%.¹³

Contrast venography

For a long time the standard test for evaluating patients with suspected DVT has been contrast venography, a gold standard against which non-invasive studies for DVT are compared. However, the current use of contrast venography is limited by the risk of pain, superficial thrombophlebitis, hypersensitivity or toxic reactions to contrast agents and interobserver variability.⁶ As a result, noninvasive studies have essentially replaced venography as the initial diagnostic test of choice.

IPG

In many studies, impedance plethysmography (IMG) has been shown to be sensitive and specific for proximal vein thrombosis.¹⁸ It is insensitive for calf vein thrombosis, non-occluding proximal vein thrombus, and iliofemoral vein thrombosis above the inguinal ligament. IPG cannot distinguish between thrombotic occlusion and extravascular compression of the vein. False-positive results occur in the setting of significant congestive cardiac failure and raised central venous pressure as well as in severe arterial insufficiency. When directly compared, duplex ultrasonography has superior sensitivity and specificity over IPG.¹⁸

CT venography

The primary utility of CT venography is for the diagnosis of iliofemoral DVT. Ultrasonography is limited to the diagnosis of DVT in the venous system distal to the inguinal ligament. The iliac veins cannot usually be visualised by ultrasonography, and a different diagnostic modality must be used. In the Prospective Investigation of Pulmonary Embolism Diagnosis II (PIOPED II) study, the addition of CT venography to CT angiography of the chest increased the diagnostic sensitivity for venous thromboembolic disease than CT angiography alone.¹⁹

MRV

Magnetic resonance venography (MRV) is the diagnostic test of choice for suspected iliac vein or inferior vena caval thrombosis when CT venography is contraindicated or technically inadequate. In suspected calf vein thrombosis, MRV is more sensitive than any other non-invasive study. However, cost, lack of general availability, and technical issues limit its use.

Conclusion

Superficial thrombophlebitis and DVT are two common peripheral venous conditions. Both are sharing the basic pathophysiology, pathogenesis and most of the risk factors. The overall incidence of venous thromboembolic diseases is increasing as the population ages, but the risk of DVT in patients with superficial thrombophlebitis is remote. The two conditions share few clinical signs, which are common to many other entities, and visual appearance is not a

reliable guide to a peripheral venous condition. The value of various diagnostic tests and imaging studies in predicting the presence of DVT depends on the likelihood of disease in each risk group. A well-validated clinical prediction rule can be used for risk stratification of patients with suspected DVT. Nowadays, non-invasive studies have essentially replaced venography as the initial diagnostic test of choice for evaluating patients with suspected DVT.

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