

## Clinical Presentation & Diagnosis of Deep Vein Thrombosis: A Literature Review

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### Abstract

**Background:** Deep vein thrombosis (DVT) refers to the formation of a thrombus, which is a blood clot, in a deep vein. Clot is usually formed in an inflamed vein, also known as thrombophlebitis. Common sites for DVT are femoral vein or the popliteal vein of the leg. DVT can lead to Pulmonary Embolism (PE), which is a serious complication of DVT. It occurs, if the clot dislodges and reaches the lungs. PE can be life threatening and therefore becomes a medical emergency. **Methods:** Electronic database was searched for related articles published online till 2018. Following key words were used 'DVT', 'D dimer', 'thrombophlebitis', 'thrombus', 'pulmonary embolism', 'deep vein thrombosis'. Studies relevant to our title were finally selected and those which failed to provide any detail were excluded from review. **Result:** DVT affects predominantly elderly population, with slight inclination towards male sex. Clinical picture of DVT is affected by the extent of obstruction to venous outflow and degree of inflammation of the vessel wall. Most of the times it is asymptomatic. Pretest probability scores in an algorithm along with D dimer testing and compression ultrasonography are used to make the diagnosis. **Conclusion:** DVT is a clinically entity with potential risk, as it can lead to pulmonary embolism. Therefore, it needs to be diagnosed as soon as possible, followed by quick intervention.

**Keywords:** DVT; D Dimer; Thrombus; Venography; Embolism.

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### Introduction

Deep vein thrombosis (DVT) refers to the formation of a thrombus, which is a blood clot, in a deep vein. Clot is usually formed in an inflamed vein, also known as thrombophlebitis. Common sites for DVT are femoral vein or the popliteal vein of the leg. Deep veins of pelvis may also be affected and sometimes even the veins of arm may be affected. The affected limb, in many patients, becomes painful, warm, swollen, red with engorged superficial veins, though DVT can also present without symptoms. DVT can lead to Pulmonary Embolism (PE), which is a serious complication of DVT. It occurs, if the clot dislodges and reaches the lungs. PE can be life threatening and therefore becomes a medical emergency.

### Methods

Electronic database was searched for related articles published online till 2018. Following key words were used 'DVT', 'D dimer', 'thrombophlebitis', 'thrombus', 'pulmonary embolism'. 'deep vein thrombosis'. Studies relevant to our title were finally selected and those which failed to provide any detail were excluded from review.

### Discussion

#### Epidemiology

##### Incidence

The exact incidence of DVT has been difficult to know, due to problems in clinical diagnosis of DVT. The 20 million cases of lower limb DVT have been estimated to occur in USA alone [1].

Patients undergoing orthopedic surgery show an incidence of 60%, with routine postoperative venography [2]. Some studies state the incidence of venous thromboembolism (VTE) is high in Asian population compared to western population [3,4]. Incidence of postoperative DVT in Indian patients, going for major lower limb is equally high as that in western population [5]. A recent study states that the incidence of acute DVT has risen from 2006 through 2010 [6].

#### *Age & Sex*

It is seen that VTE occurs after 40 years, predominantly in old age. Also, male to female ratio has been reported to be 1.2: 1 and overall age adjusted incidence rate is more for men than women [7].

#### *Pathophysiology*

Venous stasis, vessel wall injury and hypercoagulable state, together known as the Virchow triad are the primary mechanisms for development of DVT.

Which amongst them is more crucial is still debatable, but thrombus formation, its propagation and disintegration depicts a balance between the mechanism of thrombogenesis, fibrinolytic system and other circulating inhibitors of coagulation. It is observed that process of thrombogenesis is mostly activated in areas with sluggish circulation and therefore prevention of venous stasis may work as a prophylactic mechanism. The site of DVT for the lower limbs is often the deep veins of calf or within the soleal plexus.

Few cases may have involvement of ileo-femoral system due to direct injury to vessel wall from intravenous catheters or pelvic surgery. About 20% of calf vein thrombi migrate proximally before embolization, rest dissolve without intervention. It takes about 5-10 days for the thrombus to adhere and get organized, after being formed. Therefore within this time period it can propagate to other sites. There is contradictory opinion about the risk of embolization by an isolated calf vein thrombus. Amount of Risk of embolisation, attributable to a thrombus is important for diagnosis and therapeutic intervention of DVT. It is observed that the propagation and organization of the venous thrombus, damages the venous valves and venous outflow abnormalities. Less than 10% of patients experience spontaneous lysis and complete recanalization of DVT. These are important pathogenic mechanisms for development of chronic renal insufficiency.

#### *Clinical presentation*

Clinical picture of DVT is affected by the extent of obstruction to venous outflow and degree of inflammation of the vessel wall. Most patients are asymptomatic. Sometimes the thrombus does not occlude the vessel lumen significantly. Also, collaterals develop quickly and there is only slight inflammation of venous wall. On the other hand, certain nonthrombotic condition may present with similar signs and symptoms as DVT. There are no specific physical sign and symptom to diagnose DVT accurately but the clinical presentation may be as follows.

1. Edema is the most specific symptom, it occurs mostly unilaterally.
2. Leg pain is not a specific symptom, it occurs in half of the patients
3. Tenderness may be present, mostly over calf muscle or may be along the course of deep veins in thigh. Pain and tenderness may not be true indicative of the extent, site and size of the thrombus. Homans sign is sometimes seen in less than 33% of patients with confirmed DVT. Though it is nonspecific, It is demonstrated by presence of discomfort in the calf muscle on active dorsiflexion of the foot with knee straight.
4. Superficial thrombophlebitis presents with a tender, palpable, cordlike indurated subcutaneous vein. If there is no evidence of varicose veins or presence of other etiology like intravenous drug abuse or catheter, soft tissue injury, then 40% of times superficial thrombophlebitis may be associated with DVT.
5. Low grade fever may be present, high grade fever may be due to cellulitis or lymphangitis.
6. Patient may present with phlegmasia cerulea dolens, which is painful bluish inflammation due to venous engorgement and obstruction. leg may be swollen, painful and bluish in color with or without petechiae. There may be phlegmasia alba dolens, which is painful white inflammation due to iliofemoral venous thrombosis along with arterial spasm. Limb turns pale, distal pulse may be feeble or absent but it is swollen and there are distended superficial veins.
7. In 10% of patients with confirmed DVT, actually present with signs and symptoms of pulmonary embolism. In patients with confirmed PE, DVT is present in 45-70% of patients, majority of them have clinically silent DVT.

**Risk factors**

Assessment of risk factors is important in clinical evaluation of patients with suspected DVT. Without any risk factors, only 11% of patients have confirmed DVT, with 3 risk factors, 50% of patients have confirmed DVT. Risk factors related to DVT are as follows.

*General*

Immobilization more than three days, major surgery in previous 4 weeks, pregnancy and post partum period, long duration travel (> 4h) in previous 4 weeks.

*Medical*

Cancer, history of previous DVT, stroke, acute myocardial infarction, congestive heart failure, sepsis.

*Trauma*

Multiple trauma, burns, lower extremity fractures, spinal cord injury

*Vasculitis*

Systemic lupus erythematosus, Behcet syndrome, Homocystinuria.

*Hematological*

Thrombocytosis, polycythemia rubra vera, antithrombin III deficiency, Protein C Deficiency, Protein S deficiency, Factor V Leiden, Dysfibrinogenemias, disorders of plasminogen activation.

*Drugs*

Oral contraceptives, estrogens, intravenous drug abuse, heparin induced thrombocytopenia

**Clinical parameter score**

Probability of DVT is assessed with the help of *Wells Clinical Score for DVT* score for presence of various conditions.

Active cancer +1

Paralysis or recent plaster immobilization of the lower extremities +1

Recently bed ridden for > 3 d or major surgery < 4 weeks +1

Localized tenderness along the distribution of the deep venous system +1

Entire leg swelling +1

Calf swelling > 3cm compared with asymptomatic leg +1

Pitting edema (greater in the symptomatic leg) +1

Previous DVT documented +1

Collateral superficial veins (nonvaricose) +1

Alternative diagnosis (as likely or greater than that of DVT) -2

Total probability score

High probability > 3

Moderate probability 1 or 2

Low probability 0

**Investigations****Blood testing***D dimer testing*

D dimer is a product of degraded cross linked fibrin, formed by action of plasmin. D dimer represents activation of blood coagulation and fibrinolytic mechanisms [8]. DVT along with clinical evaluation is used to exclude VTE in patients with suspected DVT [9]. Studies show that D dimer can be falsely positive in various other conditions like inflammation [10], pregnancy [11] and malignancy [12]. Raised levels of D dimer amongst children with acute thrombotic events shows poor prognosis [13]. Role of d dimer in assay in early detection of suspected DVT in obese individuals has shown that the sensitivity and negative predictive value of D dimer are high [14]. D dimer levels remain high for about 7 days in DVT. Therefore, if patient presenting late, may have low levels of d dimer. Also, in patients with small clot burden the levels of d dimer will remain below the cutoff value for diagnosis. All this reduces the sensitivity of d dimer in the diagnosis of DVT. It is seen that a negative d dimer test does not require further investigation using ultrasonography [15].

D Dimer assay can be performed using different techniques, all of which have varying sensitivities and specificities. Enzyme linked immunosorbent assay is accurate though time consuming, therefore unsuitable for emergency cases. Recently available Latex-enhanced immunoturbidimetric and immunofiltration assay have high sensitivity and are being used. Older latex agglutination assay was not accurate and is not used for deciding treatment in suspected DVT cases. Rapid qualitative RBC agglutination assay is sensitive for proximal vein DVT but not so for calf vein DVT. Study shows that a negative RBC agglutination test rules out the possibility of DVT in low risk patients with low pre test probability for DVT, without the need for ultrasonography [16]. Current evidences support

the use of d dimer in investigation of suspected DVT. It is used as below.

A negative d dimer assay result rules out DVT in patients with low to moderate risk and a wells DVT score less than 2.

All patients with positive d dimer result and having moderate to high risk of DVT (Wells score more than 2) require further diagnostic study.

#### *Other blood tests*

Detection of Protein S, Protein C, antithrombin III, Factor V Leiden, Prothrombin 20210A mutation, antiphospholipid antibodies and homocysteine levels are required when DVT is diagnosed in patients younger than 50 years of age, venous thrombosis is detected at unusual site, family history of hypercoagulable state or a familial deficiency is present and in cases of warfarin induced skin necrosis. Deficiency of these factors or such abnormalities can be rare cause of DVT.

#### *Imaging studies*

It is required to be sure of the diagnosis of DVT before subjecting the patient to the risk of anticoagulation therapy. Initially the standard for evaluation of suspected DVT cases was contrast venography. But now the scenario has changed due to various problems with contrast venography like allergic reactions, contrast induced DVT, technical difficulties, interobserver variability and lack of availability. Recently noninvasive methods have replaced venography as the initial test of choice.

#### *Duplex ultrasonography*

Investigation of choice in suspected cases of DVT is venous ultrasonography. Its advantages include noninvasive, safe, available, relatively inexpensive. Different types of venous ultrasonography include compression ultrasound (B- mode imaging only), duplex ultrasound (B mode imaging and Doppler waveform analysis) and third is colour Doppler imaging alone. Compression ultrasound is better used in proximal deep veins and a combination of color Doppler and Doppler ultrasound is frequently used for calf and iliac veins (16). In case of duplex ultrasonography, Blood flow in normal vein is phasic with respiration, spontaneous and can be augmented by compression. Failure to compress the vein lumen with slight probe pressure is an important ultrasonographic criteria for detection of DVT. Complete absence of color Doppler signals from the vein lumen, response to augmentation, loss of phasic pattern in which flow is defined as continuous are the other ultrasonographic diagnostic

criteria for venous thrombosis [17]. Compression B mode ultrasonography with or without color duplex has a sensitivity of 95% and a specificity of 96% for diagnosing symptomatic, proximal DVT [18]. For DVT in calf vein, there is 73% sensitivity of venous ultrasound [19]. Symptomatic cases of DVT and in whom an alternative form of imaging is contraindicated can undergo a repeat or serial ultrasound, if initial ultrasound shows negative result. Serial ultrasound is not recommended in those with low wells score and negative D dimer test result. Pros of venous ultrasound is, no risk of exposure to irradiation, ability to differentiate venous thrombosis from hematoma, baker's cyst, abscess and other causes of leg pain and cons include less ability to diagnose distal thrombus.

#### *Contrast Venography*

Contrast venography is rarely done because of availability of noninvasive tests like d dimer and venous ultrasound, which are more accurate and appropriate. Contrast venography requires intravenous cannulation and injection of a contrast medium. A constant intraluminal filling defect in the venogram, present in two or more views, is the sign for the diagnosis of venous thrombosis [20]. An abrupt cutoff of a deep vein in venogram is another sign of thrombosis [21]. It is most useful and specific in discerning the extent, site and attachment of the thrombus. Disadvantages with this technique is invasiveness, pain, risk of allergic reactions and renal dysfunction. Also, there is chance of new thrombus formation due to irritation and endothelial damage. The risk of anaphylactic reactions and thrombogenicity has now been reduced or rather eliminated by the use of nonionic contrast medium [22,23].

#### *CT venography*

CT Venography is included in CT angiographic studies of the chest as part of the diagnostic evaluation for suspected Pulmonary Embolism. Usually scanning of the chest precedes CT venography of lower extremity, from iliac crest to popliteal fossa. CT venography is best used in diagnosis of iliofemoral DVT, as iliac vein are difficult to be visualized by ultrasonography. Iliofemoral DVT is to be considered if ultrasonographic examination shows thrombus extending to superficial femoral vein at the inguinal ligament. Disadvantages of CT venography include technical problems like artifactual interference from metal implants such as hip and knee arthroplasties.

*Impedance plethysmography*

In this method, the rate of change in impedance between two electrodes on the calf is measured, when a venous occlusion cuff is deflated. DVT is said to be present if there is delay in outflow of venous blood leading to gradual change in impedance whereas free outflow produces a rapid change in impedance [24]. Advantages of this technique are, it is safe, noninvasive, portable but it is not useful in detecting calf thrombi and nonobstructing proximal vein thrombi. Also, it can not differentiate between thrombotic occlusion and extravascular compression of the vein. There may be false positive result in case of high central venous pressure and severe arterial insufficiency.

*Magnetic Resonance Imaging (MRI)*

This technique is most useful in cases of calf and pelvic DVT and upper extremity venous thrombosis [25, 26]. Suspected iliac vein or inferior vena caval thrombosis are detected with MRI when computed tomography venography is contraindicated or technically inadequate. In Second and third trimester pregnancy cases, MRI is more accurate than duplex ultrasonography, as there is variation in Doppler venous flow characteristics by gravid uterus. MRI requires reader expertise, it is costly and not easily available.

*Nuclear medicine imaging studies*

These require longer than 24 hours and are not accurate for proximal vein thrombosis, therefore no longer recommended especially in emergency cases.

**Comparison between different tests:**

Guidelines from the American college of radiology recommend duplex Doppler compression ultrasonography to be best investigation in suspected lower limb DVT. Duplex ultrasonography is more sensitive and specific than impedance plethysmography. Also, plethysmography has a sensitivity of only 20-30% for calf vein thrombosis and requires technical expertise in procedure.

Utility of noninvasive tests like duplex ultrasonography in detecting suspected calf vein DVT is controversial. This is more relevant if anticoagulation therapy is being considered to manage calf vein DVT but not so relevant if clinical protocol involves serial studies to detect proximal extension of thrombus. The sensitivity of duplex ultrasonography for proximal vein thrombosis is very high and it is the test of choice in ambulatory

outpatients. For suspected DVT in iliofemoral DVT, CT venography is the best diagnostic test.

**Conclusion**

DVT is a clinically entity with potential risk, as it can lead to pulmonary embolism. Therefore, it needs to be diagnosed as soon as possible, followed by quick intervention.

*Key Messages*

This study reviews the clinical presentation and diagnostic approach to patients of deep vein thrombosis (DVT). DVT can lead to pulmonary embolism (PE), which is a serious complication of DVT. This article will help the readers in developing an overview of clinical presentation and protocol to diagnose DVT.

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