

## CHAPTER

# 47

# *Deep Vein Thrombosis – How and How Much to Investigate?*

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### **Introduction**

Acute deep vein thrombosis in lower limbs (DVT) is a significant but relatively under-diagnosed health problem. There is paucity of data from Indian Subcontinent, but nearly 2 million people are affected annually in the United States. The diagnosis is often missed because in many instances patients are asymptomatic and symptoms when present are not specific. Traditionally, the history and physical examination in diagnosis of a patient suspected of having DVT have been emphasized time and again, but while correlating signs and symptoms with frequency of DVT in patients with suspected thrombosis these have been found lacking in sensitivity and specificity.<sup>1-3</sup> The signs and symptoms of DVT include pain, swelling, edema and or Homan's sign. Localized pain and calf tenderness are reported in only 50% and Homan's sign in 8% to 30% of patients harboring a DVT. Furthermore, the Homan's sign can be elicited in nearly 50% of symptomatic patients who do not have a DVT as a cause of their symptoms.<sup>4,5</sup> Despite these limitations, it is important to recognize DVT because it can result in significant morbidity as well as mortality. DVT is responsible for almost 10% of deaths in hospital as a result of pulmonary thromboembolism<sup>6</sup> and in 20-50% of patients with it is associated with post-phlebotic syndrome (swelling, skin changes, venous stasis ulcers etc.) or recurrent DVT.<sup>7,8</sup> Recurrent

thromboembolism to pulmonary circuit can cause significant long-term morbidity in the form of chronic thromboembolic pulmonary hypertension. Recent years have witnessed a significant improvement in the number as well as quality of imaging technics. Some of these are expensive in term of equipment as well as need expert manpower. Therefore it is essential to have a high degree of suspicion but at the same time use investigations judiciously because of inherent costs to the patient and the hospital.

### **Diagnosis**

Because of poor diagnostic value of individual clinical features, Wells et al proposed a clinical scoring system for predicting the clinical probability of deep venous thrombosis (low, moderate, and high) (Table 1)<sup>9,10</sup> and recommended subsequent investigations based upon the risk (Figure 1). However choice of diagnostic test may be influenced by local factors including the availability of the tests as well as expertise. Diagnostic tests include D dimers, contrast venography (CV), ultrasound (USG) and computed tomography venography (CTV) and magnetic resonance venography (MRV).

### **D dimer**

D dimer is a specific degradation product released into the blood circulation when cross-linked fibrin

**Table I : Criteria proposed by Wells et al for calculating the risk of DVT**

Clinical feature	Score
1. Active cancer within 6 months	1
2. Paralysis, paresis, or cast of lower extremity	1
3. Recently bedridden > 3 d or major surgery within 4 wk	1
4. Localized tenderness along deep vein system	1
5. Calf diameter > 3 cm larger than opposite leg at 10 cm below the tibial tuberosity	1
6. Pitting edema	1
7. Collateral superficial veins (non-varicose)	1
8. Alternative diagnosis as $\geq$ likely than that of DVT	-2

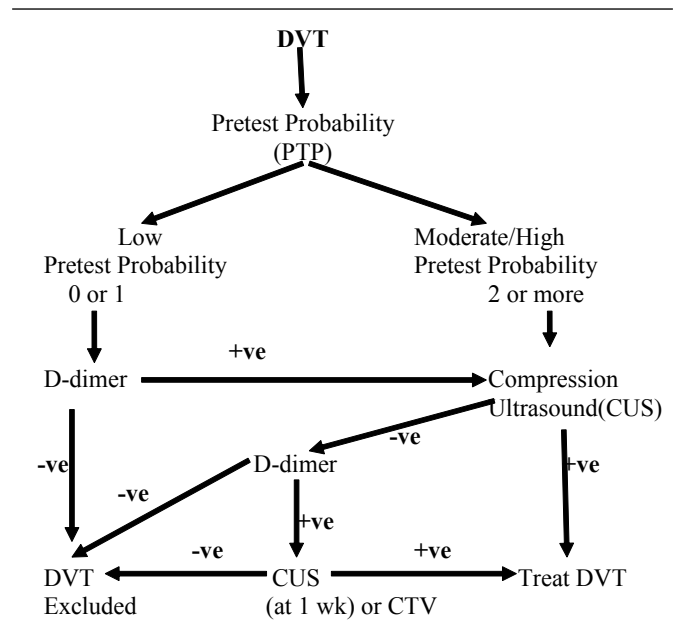
Score	Probability	Frequency of DVT(%)
0	low	03
1-2	medium	17
$\geq 3$	high	75

undergoes endogenous fibrinolysis.<sup>11</sup> Sensitivity of D Dimer is 85% to 99% and specificity is 50%–68% for above knee DVT whereas it is 85%–99% and 50%–68% respectively for below knee thrombosis.<sup>12-14</sup> However its use is limited by the variations in manufacturer's kit, method used (Latex agglutination or ELISA) and limited utility in hospitalized patients, pregnancy, cancer, and the postoperative state. D-dimers have a good negative predictive value but these can be present in several conditions mentioned earlier and in patients with systemic inflammation. Nevertheless it remains an effective screening tool. D dimer also helps in predicting the duration of anticoagulation in patients without hereditary thrombophilic states. In case D dimer's are elevated at the end of therapy, there is an increased risk of recurrent thrombosis and therefore an indication of prolonged anticoagulation.

**Contrast venography**

It is still the gold standard for DVT (sensitivity and specificity 100%) but is very rarely done these days because it is an invasive procedure and other imaging modalities attain almost the same level of accuracy.<sup>15</sup> The present day indications are

**Figure 1: Flow diagram of investigation of DVT based on wells criteria**



limited to inconclusive or impossible to perform noninvasive testing.

**Ultrasound (USG)**

The sensitivity of USG using both compression and colour doppler is between 94%–97% and specificity is 94% for above knee DVT whereas it is 64%–73% and 94% respectively for below knee thrombosis. Repeat testing at 5 to 7 days identifies another 2% of patients with clots not apparent on the first ultrasound<sup>16</sup> and also may pick up calf DVT which have been earlier missed.<sup>17</sup> Another advantage is that conditions that mimic DVT like extraluminal compression of veins from lymph nodes, tumors, abscess and ruptured baker cyst can be easily picked up. Causes for false-negative examinations include venous duplication, infrapopliteal thrombus, isolated iliac vein thrombosis and non-occlusive focal or segmental DVT. Furthermore it is limited by low pick up rates in calf vein thrombosis and DVT in obese patients. However several studies have shown higher sensitivity and specificity in patients with a high and intermediate risk score. Since only 30% of acute DVT resolve after complete therapy and nearly 50% of the patients show abnormal findings

**Table 2 : Differentiating features of acute and chronic DVT on USG**

USG Findings	Acute DVT	Chronic DVT
Atretic segments of veins	-	+
Echogenic web like filling defects within vein	-	+
Collateral Vessels	-	+
Valvular damage with reflux	-	+
Thickened walls	-	+
Venous diameter	Increased	Decreased
Calcified thrombus	-	±

on compression USG,<sup>5</sup> it becomes important to differentiate acute from chronic DVT as in the latter case no anticoagulation is required. The USG findings that differentiate acute from chronic DVT are listed in Table 2.

### CT venography

It consists of contrast-enhanced axial CT images of the upper thigh and pelvis. In a recent study it was seen that demonstrated that multislice helical CT detected DVT that had been missed by USG in five patients, but US detected DVT that was missed by CTV in one patient. The sensitivity is 95% (89%–100%) and specificity is 97% (92%–100%) for above knee and 95% (89%–100%) and 97% (92%–100%) respectively for below knee DVT.<sup>18,19</sup> When performed along with CT Pulmonary angiography (with a 3 minute delay after CTPA) it is called Indirect CTV (ICV). ICV allows examinations for both DVT and pulmonary thromboembolism in one sitting.<sup>18</sup> Besides it has an added advantage over sonography because it enables better evaluation of the pelvic veins and inferior vena cava. However the procedure currently is limited by cost and availability. In addition it cannot be performed on patients with contrast allergies, renal failure and pregnancy.

### MR venography

MRV has been recently added to the diagnostic armamentarium. The sensitivity and specificity for DVT detection were 100% for the iliac and popliteal segments and 100% and 98%, 68% and 94%, and 87% and 98%, respectively, for the

femoral, below-knee, and all vein.<sup>20</sup> In present day, it is less sensitive and specific than ICV and is more expensive but can be of utility in patients with elevated creatinine or contrast allergy. It may also be more appropriate in a pregnant woman with pelvic or iliac vein thrombosis.

From the above comparative data, it is clear that no single test is endowed with ideal properties (100% sensitivity and specificity, low cost, no risk) and often several tests are ordered, either singly, sequentially or in combination on physician preference. But combining clinical probability and D-dimer with a single USG is sensitive, specific and cost effective in diagnosing DVT.<sup>21</sup> If PTE is suspected CTPA with CTV remains a good option for diagnosing and management.

### Whom and How Much to Investigate?

In literature there is controversy regarding routinely performing bilateral lower extremity venous US examinations versus the appropriateness of performing a unilateral examination if symptoms are limited to one leg. Some studies recommend routine performance of bilateral venous USG studies of the lower extremities because thrombus can be present in asymptomatic leg as well. Some authors suggest that examination of an asymptomatic leg is unnecessary although thrombosis may occur in the asymptomatic leg in up to 14% of patients. Therefore, as on date there is no definitive consensus whether the asymptomatic contralateral leg be screened or not.<sup>22-24</sup>

After the confirmation of diagnosis of DVT, the question remains whom to investigate or how much to investigate for hypercoagulable states in a patient with DVT. Only a fraction of patients with isolated DVT will warrant extensive investigation for hereditary hypercoagulable states whereas in majority of patients a detailed history and examination along with routine investigations will suffice. The reasons being, investigations are expensive, their availability and standardisation still remains a distant dream in most hospitals in India. To add further to the confusion, certain co-morbid

**Table 3 : Effects of Comorbidity on thrombophilia tests**

Situation	AT	Protein C	Protein S
Pregnancy	↑	↓	↑
OCP use	↓	↑	↓
Acute VTE	↓	↓	↓
DIC	↓	↓	↓
Surgery	↓	↓	↓

conditions may per se interfere with the levels of thrombophilic proteins (Table 3). Thirdly, only a fraction of patients with isolated DVT will have these abnormalities<sup>25</sup> and vice versa (Table 4).

Therefore, first of all inciting factors like immobility, trauma, surgical procedures, cannulations, prolonged travel must be ruled out. Women should be diligently questioned about use of oral contraceptives and bad obstetric history. A detailed evaluation regarding drug intake is a must as certain drugs predispose to thrombosis (hydralazine, procainamide and heparin). If any of the above factor is present, there is no need for further investigations.

After excluding above factors, a search be made for acquired causes of thrombosis. These include malignancies (diminished appetite, significant weight loss, fatigue, pain, hematochezia, hematemesis, hematuria, abdominal symptoms, urinary obstruction supplemented by radiological investigations like ultrasound, chest X-ray and CT scans only if history is suggestive), collagen vascular diseases (fever, arthralgias, arthritis, rashes, renal involvement, serositis, polyneuropathies, bad obstetric history, significant weight loss), nephrotic syndrome (hypalbuminemia, frothy urine, anasarca, facial puffiness and proteinuria) and myeloproliferative diseases (splenomegaly, anemia, leukocytosis and thrombocytosis) which may be evident from history or simple biochemical, hematological or radiological investigations. Tests for hereditary hypercoagulable states are recommended in only very specific situations in cases of DVT. If the patient of DVT is less than 45

**Table 4 : % prevalence of Common inherited thrombophilic disorders and % frequency of their causing VTE**

Disorder	% Prevalence normals	% Frequency Pts with VTE
Factor V Leiden (heterozygous)	.02-4.8	18.8 7
Factor V Leiden (homozygous)	0.02	
Prothrombin mutation (G20210A)	0.6-2.7	7.1
Antithrombin III	0.02	1.9
Protein C	0.2-0.4	3.7
Protein S	0.003	2.3
Hyperhomocysteinemia (N18.5 mmol/L)	5-7	10

Data from Perry SL, Ortel TL. Clinical and laboratory evaluation of thrombophilia. Clin Chest Med

years of age without any of the above risk factors, or has recurrent idiopathic DVT, venous thrombosis at unusual sites (e.g. mesenteric venous, hepatic), warfarin induced skin necrosis, neonatal purpura fulminans or a strong family history of thrombosis preferably with documented deficiency in family or extensive thrombosis, investigations to rule out Protein C, Protein S, Antithrombin deficiency, Factor V Leiden and prothrombin gene mutation must be done. In the latter situation, even if one of the risk factors is present, it still warrants screening for thrombophilia. If there is associated arterial thrombosis, hyperhomocystinemia and antiphospholipid syndrome needs exclusion. The latter may also be accompanied by bad obstetric history, a prolonged APTT with other normal liver function tests or thrombocytopenia. Some other factors i.e. heparin cofactor II, high concentrations of factor VIII, dysfibrinogenemia, decreased levels of plasminogen activators have also been implicated but these are confined presently to research laboratories.

## Conclusion

DVT is a common problem associated with both short and long term morbidity and mortality. Therefore

it is essential to have a high degree of suspicion. Clinical signs and symptoms lack sensitivity and specificity. In cases of suspected DVT, D dimers and USG should be included in diagnostic work up followed by CTV, if the situation demands. After confirming the diagnosis an attempt must be made to look for the etiology. History, examination and routine investigations help to rule out the acquired coagulable states. Since only 30% of patients have inherited thrombophilias, search must be made in certain select group of patients with DVT.

## Summary

Deep venous thrombosis (DVT) is a common medical problem with a potential for significant morbidity and mortality. However because of lack of symptoms or the lack of specificity of the signs and symptoms, this remains under-diagnosed in many instances or till very late when the thromboembolic complications become clinically evident. Even though the clinical signs and symptoms are said to be non-specific and nonconfirmatory, clinical scoring systems that take symptoms, signs and risk factors into considerations help in assigning a clinical risk and further help in choosing the investigations to confirm the diagnosis. Investigations for DVT are generally directed towards confirmation of the venous thrombosis, identifying embolic phenomena and factors responsible for DVT that may have a bearing on the long term management. Of several investigating modalities for confirmation of DVT a judicious use of blood test for D-dimers as a negative predictor and ultrasound and doppler imaging is adequate for making the initial diagnosis. With improvement in imaging technics, lower limb venography is not needed for most patients. Advanced imaging technics may be needed for confirmation of venous thrombosis at unusual sites like mesentery, cerebral cortical venous system etc. In young patients with unprovoked DVT tests for underlying thrombophilic state would be needed. However, it is important to recognize that many tests are affected by active thrombosis or its treatment and also that treatment takes precedence

over establishing the cause. It may be prudent to carry out tests based on biological activity after completing the treatment.

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