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Venous thromboembolism: the role of the clinician

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ABSTRACT Deep venous thrombosis is a diagnosis that should be considered in any patient who presents with a swollen or painful leg. Clinical examination alone has low sensitivity and specificity for detecting patients with clots, and in recent years a diagnostic pathway has been devised that is more effective. This involves integration of three modalities: clinical assessment, D-dimer analysis and ultrasound. The management of a patient found to have a deep venous thrombosis includes immediate treatment but also the consideration of risk factors, family history, need for thrombophilia testing, duration of treatment and the prevention of post-thrombotic syndrome.

KEYWORDS D-dimer, deep vein thrombosis, diagnosis

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Venous thromboembolism (VTE) is one of the most common medical conditions faced by physicians in both primary care and hospital-based medicine. It is estimated that 5% of people in their lifetime are affected, with an annual incidence of approximately one in 1,000 for deep venous thrombosis (DVT) and one in 3,000 for pulmonary embolism (PE). This is highly age dependent, with young adults having an incidence of approximately one per 10,000, rising to as high as one in 100 in the elderly.

Venous thromboembolism is a common cause of morbidity and mortality (the case fatality is approximately 5%). Post-mortem studies suggest that pulmonary embolism is responsible for 10% of deaths in hospitalised patients. Post-thrombotic syndrome can affect up to one-third of patients with a DVT and can even present as late as ten years from the original diagnosis, leading in some cases to considerable reduction in quality of life. Recurrence of VTE is also common, with figures as high as 25% at five years.

An increasing awareness of the diagnostic pitfalls and sequelae of VTE has led to many more patients being referred for assessment. Since the introduction of low molecular weight heparin (LMWH) as treatment for VTE, the assessment and diagnosis of patients is often nurse-led in specific DVT outpatient clinics.

DIAGNOSIS

Thirty to forty years ago, DVT was diagnosed simply by clinical judgement, with no additional testing. Since patients can present in a variety of non-specific ways this method was fraught with problems. It has been estimated that this approach misdiagnosed patients in up to 50% of case, either putting them at unnecessary risk of bleeding from anticoagulation or at risk of a potentially fatal PE. Since then clinical medicine has seen a revolution in the diagnosis of DVT with the use of an integrated system: this includes clinical assessment, laboratory testing (in the form of D-dimer analysis) and diagnostic radiology. This combined approach to diagnosis has been demonstrated to be extremely effective.

TABLE 1 Pre-test probability assessment (Wells' score)

	Points
Active cancer (treatment ongoing or within previous six months or palliative)	1
Paralysis, plaster	1
Bed ≥3 days; major surgery within 12 weeks	1
Tenderness along veins	1
Entire leg swollen	1
Calf swollen >3 cm	1
Pitting oedema	1
Collateral veins	1
Previous DVT	1
Alternative diagnosis likely	–2

DVT unlikely: ≤1. DVT likely: ≥2.

Algorithm for DVT diagnosis

The initial step for patients presenting with a possible DVT is to assess them for their individual pre-test probability, i.e. the likelihood that they have a DVT. This involves using a scoring system such as the updated Wells' scoring system, in which a patient is assessed using history and examination to answer the points shown in Table 1. The resulting score has been used to stratify patients as 'low', 'moderate' or 'high' risk or more recently as 'likely' or 'unlikely' to have a DVT.

The next step is dependent on the patient's pre-test probability score (please refer to Figure 1 to follow the

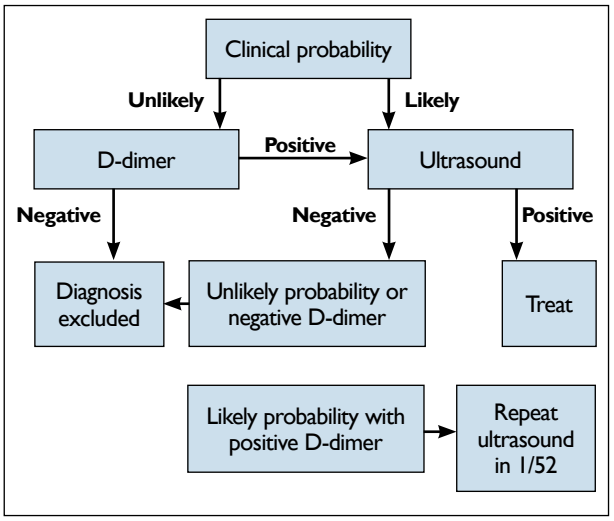

FIGURE 1 One possible diagnostic algorithm for non-pregnant patients with a suspected DVT based on the recommendations.

diagnostic algorithm for the management of patients). Patients scoring as an 'unlikely' risk should have a D-dimer assay performed. If this result is negative, the patient can be safely discharged without further assessment. If, however, the result is positive the patient should be sent for an ultrasound scan (USS).

In some primary care centres, general practitioners perform D-dimer assays and can therefore reduce the workload of potential DVT patients reaching hospital. These assays should only be done in centres that are performing pre-test probability assessments and are using validated D-dimer assays.

If patients fall into the 'likely' risk category, they should have a USS. A D-dimer assay is then only checked in patients if their ultrasound has been unable to detect a clot. A negative D-dimer enables a patient to be discharged, but a positive result should lead to a repeat scan six to eight days later. This is recommended practice in case an undetected distal DVT has extended above the knee. Distal DVTs that do not extend above the knee rarely lead to clinically significant emboli, and those that extend usually do so within the first week. If a repeat USS is negative at seven days, the patient may be discharged.

This algorithm was not validated for patients presenting during pregnancy. These patients should undergo investigation with USS.

D-dimer

D-dimer is a breakdown product of cross-linked fibrin and is elevated in acute VTE. D-dimer assays detect these products and a positive result may therefore indicate the presence of a clot. However, in reality, D-dimer assays are much more useful as a negative predictor to rule out DVT rather than to confirm a suspicion.

TABLE 2 Pitfalls of D-dimer testing

False positive D-dimer result	False negative D-dimer result
Inflammation	Heparin use
Elderly	Symptoms longer than 2 weeks
Malignancy	Small below-knee DVT
Pregnancy	

The best D-dimer assays currently available are based on enzyme-linked immunosorbent assay (ELISA) methods, and these tests are highly sensitive (approximately 98%) but have a low specificity for VTE (around 45%) and therefore can often provide false-positive results (see Table 2). D-dimer assays are more frequently raised in elderly patients and therefore less often exclude the diagnosis. It is also important to note that heparin use has been shown in several studies to cause a fall in D-dimer levels, and we would only recommend D-dimer testing prior to heparin administration.

Radiological input

Compression ultrasound

This non-invasive, simple diagnostic test is the mainstay of radiological diagnosis of DVT. Patent veins can be compressed, but those that contain clot are incompressible. For proximal DVT, ultrasound has been shown to have a sensitivity of 97% for patients presenting with their first onset of symptoms, with a specificity of 98%. Doppler imaging does not increase this level of accuracy. Ultrasound is not as sensitive for detecting below-knee DVTs (73%) and most diagnostic strategies rely on serial ultrasound when indicated and do not look for distal DVT.

Contrast ascending venography

Although this technique is still viewed as the gold standard for diagnosis of a limb DVT, it is used infrequently. The technique involves cannulation of a pedal vein followed by injection of contrast media (volume: 50–150 ml). Venography can detect both above- and below-knee DVTs, but it is invasive and can be painful. Cannulation can also be difficult in patients with swollen extremities, with failure rates as high as 12–14%. In addition, in up to one-quarter of studies results are incomplete owing to poor visualisation of pelvic veins or inability to visualise the upper limit of the thrombus. Occasionally a venogram can induce DVT after a negative result, due to vein wall irritation.

MANAGEMENT OF DVT PATIENTS

Once a patient has been diagnosed with a DVT, the following issues must be considered:

- *Anticoagulation*. This should be commenced. For the majority of patients, treatment is with LMWH and

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warfarin together for five days or until the international normalised ratio (INR) is within range for at least 48 hours, whichever is the longer. Low molecular weight heparin can then be stopped. However, for some, LMWH with no accompanying warfarin is the optimal choice, in particular for patients with active malignancy or during pregnancy (in which warfarin is contraindicated).

- *Duration of therapy*. This is beyond the scope of this article, but the key decision is whether to treat for a finite period (of at least three months) or to recommend long-term anticoagulation which would be considered for:
  - Recurrent thromboses
  - Patients with an ongoing risk factor such as active cancer
  - A first unprovoked proximal DVT or PE where there are no risk factors for bleeding and where anticoagulant control is good.[1] This may be felt to be particularly the case:
    - if D-dimers are raised after discontinuing anticoagulation
    - in a male
    - in those with post-thrombotic syndrome (PTS)
    - in those with antiphospholipid antibodies.

Compression stockings have been shown to reduce the rate of PTS by as much as 50% if worn for a period of at least two years.

It is also important to remember that 6% of seemingly unprovoked DVT patients will have undiagnosed cancer at presentation, increasing to 10% in the first year thereafter. A recent study estimated that 50% of such cancers would be detected by a history, physical examination and basic tests, such as a full blood count, liver function tests and chest X-ray, and that this would be increased to 70% with a computed tomography scan of the abdomen and pelvis.[2] This has not been shown to be cost-effective and is not routine in most centres.

Thrombophilia testing

Many patients who present with their first DVT will not require thrombophilia testing. It should be considered if it might help the management of the patient or have significant implications for the family. This is more likely to be the case if the patient has first-degree female relatives of child-bearing age.

Thrombophilia testing should ideally be overseen by the haematology department, and local guidance followed.

Inferior vena caval filters

Inferior vena cava (IVC) filters are rarely needed and should only be used after careful consideration. If possible, retrievable devices should be used. Inferior vena cava filters are suitable for use in patients who are at high risk of a pulmonary embolism but at the same time have a contraindication to anticoagulation. They may also be considered in those patients who develop PEs while on anticoagulation.

Patients undergoing surgery within one month of a diagnosis of a DVT may be candidates for an IVC filter while anticoagulation is discontinued, and pregnant women who develop extensive VTE within two weeks of delivery may be considered for a temporary filter.

Prophylactic treatment

There have been many published reports over the past few years that have highlighted the risk to hospitalised patients, both surgical and medical, of developing VTE. The chief medical officer in England has said that all patients admitted to hospital should have their need for prophylactic anticoagulation assessed and a risk assessment model has been proposed.[3] If prophylaxis is indicated this is usually administered as LMWH.

New anticoagulants

Warfarin has been the oral anticoagulant of choice for many years but requires blood test monitoring. New oral direct thrombin inhibitors and factor X inhibitors are currently undergoing evaluation in large phase three studies. These drugs have the advantage of relatively few drug interactions and do not require blood monitoring. It is possible that they may be widely available in a few years' time.

KEY POINTS

- Deep vein thrombosis is a common diagnostic problem.
- Risk stratification of patients using a simple algorithm aids diagnosis and reduces the numbers of patients requiring ultrasound scans.
- D-dimer assays are a useful negative predictor of deep vein thrombosis.
- Underlying causes should be sought in patients with unprovoked deep vein thrombosis.
- The requirement for long-term anticoagulation should be decided on an individual basis.

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EDUCATION

SELF-ASSESSMENT QUESTIONS

1. A 38-year-old man presents with a swollen right leg. Examination reveals a significantly swollen calf with pitting oedema. He had undergone an appendectomy six weeks previously. Which ONE of the following is the next step?

A. D-dimer assay; if this is positive proceed to ultrasound.
B. Ultrasound; if this is negative discharge the patient.
C. Ultrasound; if this is negative repeat the ultrasound in 6–8 days.
D. Ultrasound; if this is negative check D-dimer assay and repeat the ultrasound if assay positive.
E. D-dimer assay; if negative discharge patient.

2. Which ONE of the following situations would not usually give rise to a positive D-dimer result?

A. Pregnancy.
B. Uncomplicated asthma.
C. Elderly patient.
D. Malignancy.
E. Pneumonia.

3. Which ONE of the following patients would not need to be considered for long-term anticoagulation?

A. A patient with proven recurrent deep vein thromboses (DVTs).
B. A patient with a first DVT with known lung cancer.
C. A patient with a first DVT after a hemicolectomy.
D. A patient with a first unprovoked DVT and raised D-dimer assay at the end of anticoagulant therapy.
E. A patient with antiphospholipid syndrome and a proximal DVT.

4. A 72-year-old man is reviewed in pre-operative assessment prior to a total hip replacement. He suffers from diabetes and is a lifelong smoker. Which ONE of the following is the most appropriate form of thromboprophylaxis?

A. Anti-thromboembolic compression stockings alone.
B. Compression stockings and low molecular weight heparin (LMWH) at doses of 2,500 IU dalteparin or 20 mg enoxaparin.
C. Compression stockings and aspirin.
D. Compression stockings and LMWH at doses of 5,000 IU dalteparin or 40 mg enoxaparin.
E. Compression stockings and low-dose warfarin.

5. A 40-year-old woman, with known recent carcinoma of the breast, is reviewed in clinic following a diagnosis of her first proximal DVT. Which ONE of the following is the correct management regarding anticoagulation?

A. Therapeutic LMWH or warfarin for six weeks.
B. Warfarin, INR 2–3 for three months.
C. Warfarin, INR 2–3 for six months and consideration of extended anticoagulation beyond six months during treatment for her cancer.
D. Therapeutic LMWH for three months.
E. Therapeutic LMWH for six months and consideration of extended anticoagulation beyond six months during treatment for her cancer.

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