Adv Exp Med Biol - Advances in Internal Medicine (2016)
DOI 10.1007/5584_2016_103

The Diagnosis and Management of Early Deep Vein Thrombosis

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Abstract

The diagnosis and management of an acute DVT is difficult and mistakes are often made. The cost to the National Health Service (NHS) of litigation arising from failure to diagnose and treat DVT early is substantial. Clinical diagnosis alone is often unreliable and a large proportion of DVT occurring in hospital are asymptomatic. In the United Kingdom, clinical scoring systems, D-dimer and ultrasound (US) imaging have all been adopted to aid diagnosis via DVT pathways. These pathways aim to exclude DVT only and often fail to actually address the cause of the symptoms once DVT is eventually cleared.

Keywords

Deep vein thrombosis • Venous thromboembolism • Swollen leg • Diagnostic pathway

1 Introduction

Acute leg swelling is a common presentation to Accident and Emergency (A&E) departments and General Practitioners (GP) in the United Kingdom. As well as a major concern for the patient, it is a difficult presentation to manage for clinicians and requires careful consideration to its aetiology and subsequent management. Lower limb swelling can often be a manifestation of a chronic underlying disease which has become symptomatic or represent a more acute problem which may be life threatening; therefore determining whether the swelling is acute or chronic should be the first step in assessing this common presentation.

Deep vein thrombosis (DVT) is a common cause of morbidity and mortality. The annual incidence of DVT of the leg is between 48 and 182 per 100,000 in the population (Khanbhai et al. 2015). It is the most worrisome of the aetiologies of acute leg swelling and prompt diagnosis and management is essential to minimise the risk of pulmonary embolus (PE) and post thrombotic syndrome (PTS).

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This chapter reviews the diagnosis and early management of DVT. It also describes common aetiologies for acute leg swelling once DVT has been excluded.

2 Pathophysiology

Virchow's triad describes three factors which increase the propensity to thrombogenesis (venous stasis, intimal damage and hypercoagulability). Many of the risk factors for DVT are related to venous stasis such as immobility, obesity, pregnancy, and trauma. Although direct intimal damage is rare, external trauma to a vein such as during pelvic or lower limb surgery can instigate thrombogenesis. Hypercoagulability is often suggested in young patients (<45 years) with a family history of venous thromboembolism.

Often beginning in the calf, the clot is free-floating within the vein and it is at this point that risk of pulmonary embolism is highest. The clot then becomes densely adherent to the vessel wall and incites an inflammatory reaction. It is at this point that the DVT becomes clinically apparent with leg swelling, dilated superficial veins and pain.

3 Diagnosis of DVT

The diagnosis of DVT of the leg can be difficult with clinical findings and history being unreliable. The National Institute of Health and Care Excellence (NICE) has evidence-based recommendations on the prevention and management of a wide range of health conditions. NICE published guidance on the detection and subsequent management of DVT and suggests the incorporation of a clinical prediction score (Wells score), d-dimer test and venous duplex ultrasound (Figs. 1 and 2) (Venous thromboembolic disease: the management of venous thromboembolic disease and the role of thrombophilia testing; Treating venous thromboembolism).

3.1 The Wells Score

NICE recommend the use of the two-level DVT Wells score to estimate the clinical probability of DVT as shown in Table 1. Patients with a score of 2 points or more should be offered a venous duplex ultrasound scan carried out within 4 h of being requested. If a venous duplex ultrasound scan is not available within 4 h of being requested, a D-dimer test and interim 24 h dose of parental anticoagulation is suggested.

3.2 Duplex Ultrasound

Venous duplex ultrasound has been widely adopted as the first line investigation for suspected DVT. It is able to identify DVT of the leg with a sensitivity of 96.5 % for proximal (above knee) DVT and 71.2 % for calf DVT, both with a specificity of 94 % (Goodacre et al. 2005).

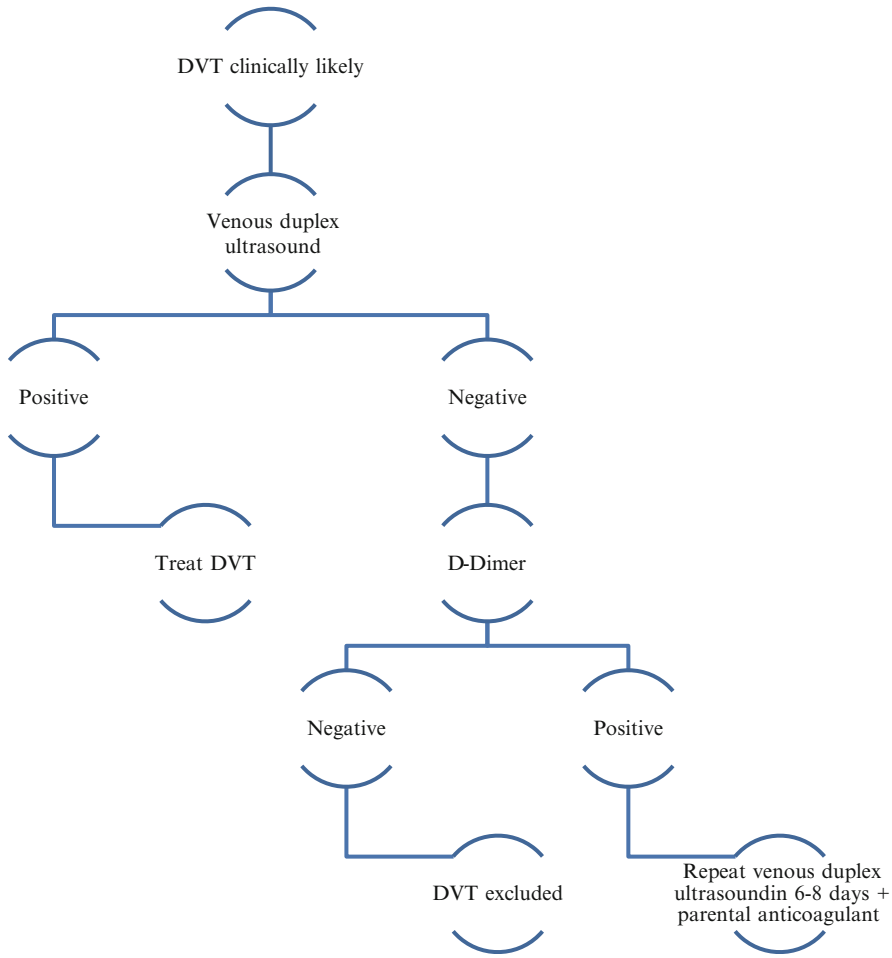
A screening two-point ultrasound is often used in clinical trials to detect the possibility of DVT in asymptomatic patients. Compressibility of the deep veins at two points (the common femoral and the popliteal veins) can characterise the scan as normal (fully compressible), abnormal (non-compressible) or non-diagnostic (due to poor images). This two-point screening test has been shown to be sensitive and specific (Robinson et al. 1998). However it will not detect below knee or non-occlusive proximal (iliac) DVT. Abnormal and non-diagnostic examinations are usually followed up by a complete diagnostic venous duplex ultrasound which includes B-mode imaging for compressibility and visualisation of the thrombus, spectral display to determine flow direction and respiratory phasicity and colour-flow imaging to determine flow. Virtually all vascular labs use the inability to collapse a vein with probe pressure as the primary diagnostic criteria for DVT. A recent RCT showed that the two-point and whole leg strategies are equivalent in identifying DVT in symptomatic patients but despite this screening two-point ultrasound is not routinely used in clinical practice (Bernardi et al. 2008).

The venous duplex ultrasound can be repeated 6–8 days later in patients with persistent swellings, a positive D-dimer and an initial negative duplex ultrasound. Most DVT algorithms and duplex ultrasound protocols for DVT only include initial ultrasound evaluation of the proximal leg veins only even in symptomatic patients. This is largely based on out-dated perceptions that ultrasound examinations of the calf veins are inaccurate and such strategies are inefficient and not cost-effective. With the commonest site for DVT being the muscular calf vein, scanning the proximal veins will invariably miss a large proportion of DVT (Yoshimura et al. 2012; Zierler 2004).

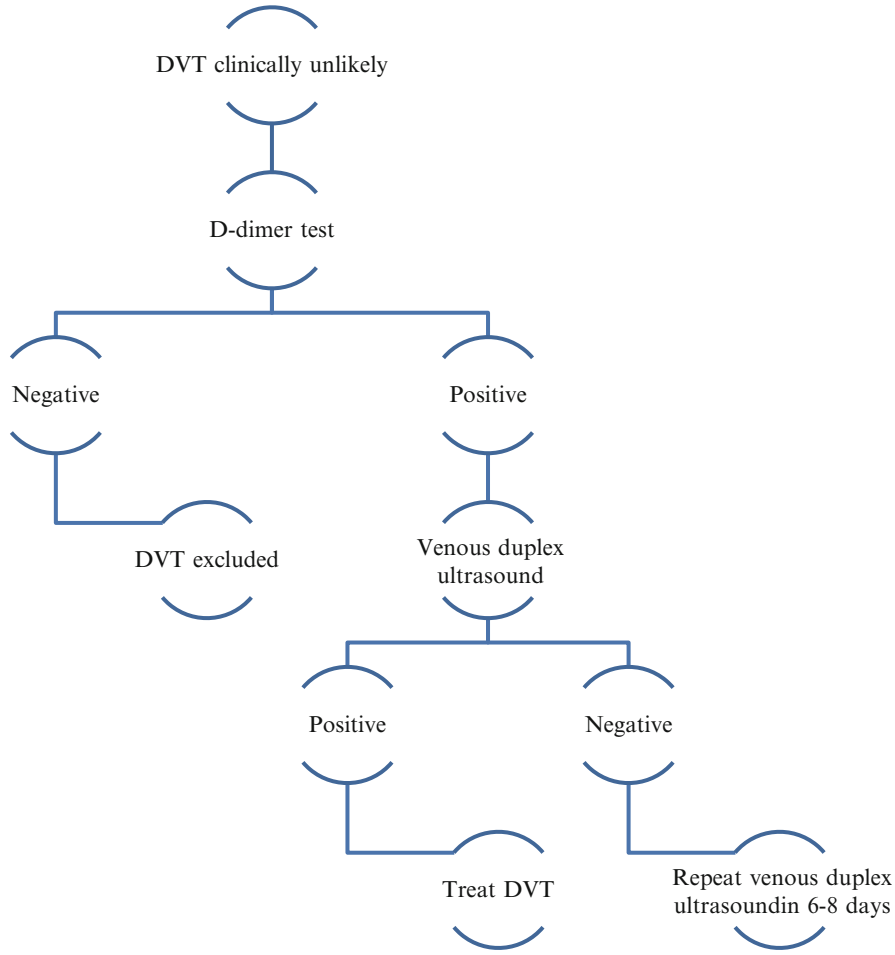
The duplex examination can also be useful to help determine the cause of leg pain and swelling when a DVT is excluded. Intramuscular hematomas, Bakers cysts and varicose vein disease can mimic DVT and be identified on duplex ultrasound.

3.3 D-Dimer Test

In patients in whom DVT is suspected and with a low Wells score, a D-dimer test is suggested. The use of the D-dimer test to rule out DVT and remove the need for more expensive testing has increased in popularity over the last decade.



Figs. 1 and 2 Illustration of diagnostic approach for suspected DVT



Figs. 1 and 2 (continued)

Table 1 Two-level DVT wells score (Wells et al. 2003)

Clinical feature	Points
Active cancer (treatment ongoing, within 6 months, or palliative)	1
Paralysis, paresis or recent plaster immobilisation of the lower extremities	1
Recently bedridden for 3 days or more or major surgery within 12 weeks requiring general or regional anaesthesia	1
Localised tenderness along the distribution of the deep venous system	1
Entire leg swollen	1
Calf swelling at least 3 cm larger than asymptomatic leg	1
Previously documented DVT	1
An alternative diagnosis is at least as likely as DVT	−2
Clinical probability simplified score	
DVT *likely*	2 points or more
DVT *unlikely*	1 point or less

D-dimers are degradation products produced as a result of plasmin on cross-linked fibrin indicating the development of a thrombus. There are however several other conditions that can elevate D-dimer results such as infection, myocardial infarction, malignancy, trauma and pregnancy which make its interpretation difficult (Schumann and Ewigman 2007).

D-dimer test can reliably exclude DVT with a 99 % negative predictive value (Wells et al. 2003). Patients with a high Wells score with a negative venous duplex ultrasound scan are recommended to have a D-dimer test. A negative proximal ultrasound scan and D-dimer can reliably exclude DVT. In practice where a D-dimer test will not provide a reliable result, duplex ultrasound remains as the most robust diagnostic tool.

3.4 Venography

Catheter-based contrast venography had traditionally been accepted as the reference diagnostic test for DVT before the widespread introduction of duplex ultrasound. Contrast venography was up until recently still widely used in clinical trials investigating anticoagulant therapies (Eriksson and Quinlan 2006). Because of its invasive nature, technical difficulty and cost it is not deemed suitable for routine clinical evaluation of suspected DVT (Zierler 2004). It is however still used for suspected pelvic and iliac vein DVT.

Magnetic resonance venography (MRV) is an alternative to catheter-based venography and has been shown to be highly accurate with sensitivies of 97 % and specificity of 100 % with excellent inter-observer variability for iliac, femoral and below knee DVT (Fraser et al. 2002; Spritzer et al. 2001). Compared with conventional catheter-based contrast venography, it is non-invasive and avoids ionising radiation. It is however expensive compared to venous duplex ultrasound and not available to patients with metal implants.

Computerised tomographic (CT) venography is similarly advantageous as MRV over duplex ultrasound but does involve ionising radiation and the use of intravenous contrast. It is reported to be 97 % sensitive and 100 % specific at determining lower limb DVT compared with duplex ultrasound (Frankel and Bundens 2014).

4 Management of Early DVT

4.1 Anticoagulation

The aim of treatment for DVT is to relieve the acute symptoms whilst reducing the risk of recurrent thrombosis and post-thrombotic syndrome. The initial anticoagulant regime for DVT can be a choice of either intravenous or subcutaneous un-fractionated heparin (UFH), low molecular weight Heparin (LMWH), Fondaparinux, Rivaroxaban and Apixaban. Vitamin K antagonists such as Warfarin can be initiated simultaneously with heparin to a target international normalised ratio (INR) of 2.0–3.0 In the UK LMWH in the form of Enoxaparin, Dalteparin or Tinzaparin are most frequently used in hospitalised patients whilst the target INR is reached. It is favoured because it can be administered by a single daily subcutaneous injection and is less likely to produce heparin related thrombocytopenia when compared to UFH. There are several LMWH on the market some of which are licensed for treatment and pharmacological VTE prophylaxis; prescribers must review local hospital guidance on which agent to use.

New oral anticoagulants such as Rivaroxaban and Apixaban are now recommended for use in the treatment of acute VTE in adult patients after review by NICE in 2012 and 2015 respectively. Both drugs have been shown to be clinically more effective and cheaper for patients requiring anticoagulation for longer than 12 months as they remove the need for regular monitoring and blood tests (Rivaroxaban for the treatment of deep vein thrombosis and prevention of recurrent deep vein thrombosis and pulmonary embolism). A recent meta-analysis of new oral anticoagulants (Dabigatran, Rivaroxaban, Apixaban and Edoxaban) showed that they significantly reduced the risk of stroke or systemic embolic events by 19 % when compared with warfarin (RR 0.81, 0.38–0.64, $p < 0.0001$) but was associated with greater risk of gastrointestinal bleeding (Ruff et al. 2014). No clinically

Table 2 Recommended duration of anticoagulation (Kearon et al. 2008)

Patients	Modifier	Recommendation
1st episode distal DVT	Idiopathic or unprovoked	3 months
1st episode proximal DVT	Idiopathic or unprovoked	Consider Long term (indefinite) therapy
1st episode DVT	Transient risk factor (long travel, post-operative, lower limb immobilisation)	3 months
2nd episode (distal or proximal) DVT	Idiopathic or unprovoked	Consider Long term (indefinite) therapy
1st episode DVT	Cancer	LMWH for 3–6 months and anticoagulation as long as cancer is active
1st episode DVT	Antiphospholipid antibody or $\geq$2 thrombophilic conditions	Indefinite anticoagulation
Recurrent DVT		Indefinite anticoagulation

relevant increases in major bleeding events were noted in the RE-COVER, RE-MEDY and the EINSTEIN trials that established the efficacy of dabigatran and rivaroxaban for the prevention of VTE (Sarrazin 2015).

Vitamin K antagonists include substances with a short (acenocoumarol), intermediate (warfarin, fluindione), or long (phenprocoumone) half-life. Because of the variable vitamin K content of food, a narrow therapeutic index, and several interactions with other drugs, treatment with vitamin K antagonists needs close monitoring. The safety their use can be increased by encouraging compliance, avoiding use of concurrent drugs with potential interactions, and restricting alcohol intake.

The duration of oral anticoagulant depends upon patient presentation, history of prior venous thromboembolism and condition of the patient after 6–12 months of therapy. The American College of Chest Physicians (ACCP) recommendations for duration are summarised in Table 2 but the optimal duration is still uncertain. Co-morbidities, family history, BMI and gender all need to be taken into account before stopping anticoagulation. Serial D-dimer testing to determine the risk of recurrent DVT has been shown to produce promising results in large cohort studies. Patients with abnormal D-dimer levels 1 month after discontinuation of anticoagulation were shown to have significantly higher incidence of recurrent VTE compared to patients with persistently negative D-dimers after stopping anticoagulation (Palareti et al. 2006, 2014).

4.2 Post Thrombotic Syndrome

Post thrombotic syndrome (PTS) is a chronic condition that develops in 25–50 % of patients after DVT. Often presenting with leg pain, chronic oedema, skin discolouration and ulcers it is associated with significant health and economic burden as reduces quality of life. PTS develops due to either valvular incompetence or residual outflow obstruction with eventual calf muscle pump failure after DVT. Therefore treatment of the primary DVT should be aimed not only at preventing thrombus propagation and PE, but also on preventing venous damage and restoring venous function. This may include limb elevation, elastic compression therapy and in some cases thrombolysis.

All patients who have had a DVT should be considered for long-term elastic compression hosiery, in particular those who are on their feet all day or travel long journeys. They should also be encouraged to take regular exercise to stimulate the calf muscle pump. Graduated elastic compression stockings (ECS) applied after initiating coagulation is thought to reduce the development of PTS is not associated with increased risk of PE. Previous studies have demonstrated that wearing ECS could reduce post-thrombotic morbidity by up to 50 % (Partsch 2005; Brandjes et al. 1997) but a recent multicentre randomised control trial showed ECS did not prevent the development of PTS when compared to a placebo; incidence of PTS 14.2 % in patients with ECS compared with 12.7 % in

placebo ECS (Kahn et al. 2014). Although the development of post thrombotic syndrome may not be prevented by ECS it may still be effective in the management of its symptoms and warrants further assessment in future studies.

4.3 Severe or Complicated DVT

iliofemoral DVT, vena cava, phlegmasia or recurrent thrombosis may be considered for thrombolysis or caval filter insertion. Catheter-directed thrombolysis can rapidly clear the thrombotic segment in patients with extensive proximal DVT. It is considered in patients who have a high proximal DVT, good functional status, a life expectancy of 1 year or more and a low risk of bleeding as it has been shown to be associated with more frequent adverse events and bleeding but no difference has been shown in mortality when compared with anticoagulation alone (Enden et al. 2012). Accepted indications for caval filter insertion include cases where it can be proved that PE is still occurring despite adequate anticoagulation or where anticoagulation is contra-indicated. Filters are inserted under local anaesthesia percutaneous through the jugular or femoral vein.

4.4 Unprovoked DVT

Patients who have developed an unprovoked DVT or PE who are not already known to have cancer should be offered further investigations. This includes a physical examination, a chest X-ray, blood tests and urinalysis to identify undiagnosed malignancy. Further investigations using abdomino-pelvic CT scan in patients over 40 years may also be warranted.

Thrombophilia testing should be offered in patients with an unprovoked DVT or PE. In particular if it is planned to stop anticoagulation. Hereditary thrombophilia testing in patients who have a first degree relative with DVT or PE is also suggested by NICE (Treating venous thromboembolism).

5 Alternative Causes of Acute leg Swelling

Common causes of both acute and chronic leg swelling are shown in Table 3. A careful and systematic history and physical examination will point to the likeliest aetiology.

5.1 Chronic Venous Insufficiency (CVI)

CVI is the most common cause of lower limb swelling in the elderly, often due to primary valvular incompetence or secondary to DVT, but almost invariably associated with obesity or poor mobility. Sitting for prolonged periods of time they are exposed to almost continuously raised venous pressure at the ankle. This venous hypertension leads to oedema which is initially pitting but can progress to subcutaneous fibrosis and induration. In the obese, the femoral vein and lymphatics in the groin are compressed between the fat of the lower abdomen and the thigh on sitting. This compression alone may cause prolonged swelling and even ankle ulceration, even in patients with healthy veins.

Table 3 Shows the causes of swelling of the lower limb

Acute	Chronic
Deep vein thrombosis (DVT)	Venous disease: post thrombotic syndrome, lipodermatosclerosis, chronic venous insufficiency, venous obstruction
Cellulitis	
Superficial thrombophlebitis	Lymphedema: cancer treatment, infection, tumour, trauma, pretibial myxoedema
Joint effusion or heamarthrosis	
Haematoma	Congenital vascular abnormalities: haemangioma, klippel-trenaunay syndrome
Musculoskeletal	Others: heart failure, reflex sympathetic dystrophy, idiopathic oedema in women, hypoproteinaemia in cirrhosis or nephrotic syndrome, armchair legs, lipoedema

5.2 Lymphedema

Lymphedema is a condition in which excessive amounts of protein-rich fluid accumulates in peripheral tissues. The lymphatic system removes excess water and protein from the interstitial space. Intrinsic lymphatic contractions and endothelial valves direct flow centrally, with lymph entering the venous system through the thoracic duct. Lymphoedema is a chronic condition which can be managed effectively if a careful treatment program is followed.

Early or new onset lymphedema can present with pitting oedema. Swelling often commences distally on the foot and extending proximally either uni- or bilaterally. Often difficulties with footwear is the first sign that patients notice. It is often reversible at this stage and may be managed by high leg elevation and compression hosiery. Focal pain is not a characteristic of lymphedema, although patients may complain that the limb is heavy.

5.3 Cellulitis

Painful, erythematous, red unilateral leg oedema with increased warmth suggests cellulitis. A careful search often reveals a break in the skin integrity allowing bacterial ingress. Predisposing factors should be sought, such as foot blisters, skin excoriation and previous episodes of cellulitis.

5.4 Musculo-Skeletal

Sudden intense pain of the posterior lower leg is often suggestive of a musculoskeletal cause. If pain was associated with sudden dorsiflexion of the foot, rupture of the tendinous portion of the gastrocnemius or plantaris muscle should be suspected. Localised swelling in the mid-calf area is also common. Ecchymotic discolouration can follow 2–5 days later.

Popliteal cyst rupture can present with sudden severe pain and swelling of the calf. Popliteal cysts are composed of a fibrous wall communicating with the joint space and lined by synovia and often develop as a result of degenerative arthritis, trauma and gout. Popliteal cysts are can cause chronic symptoms of discomfort. Symptoms include posterior knee pain and swelling, tenderness on palpation with a palpable mass. The diagnosis is uniformly made with a duplex ultrasound examination.

Treatment of musculo-skeletal pain is symptomatic, applying cold packs or ice, anti-inflammatory medications reduced weight bearing and treatment directed at the underlying condition.

6 Conclusion

The acutely swollen limb is a common presentation with several causes, the most worrisome being DVT. This chapter has highlighted the pathway used to diagnose and manage early DVT. It is imperative that duplex ultrasound is used almost primarily to diagnose or exclude DVT. Once DVT is excluded, patients with persistent symptoms an alternative diagnosis should be sought.

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