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Deep vein thrombosis
Risks and diagnosis

Background
Venous thromboembolism, comprising deep vein thrombosis (DVT) and pulmonary embolism, is common in Australia and is associated with high morbidity.

Objective
This article provides a summary of the risk factors for DVT of the lower limb and discusses the diagnosis of the condition using a diagnostic algorithm incorporating clinical assessment, D-dimer testing and imaging studies. It also briefly reviews the clinical significance of isolated distal lower limb DVT and superficial vein thrombosis.

Discussion
Many conditions in the lower limb mimic DVT. Diagnosing DVT on clinical grounds without objective testing is unreliable. Patients incorrectly diagnosed as having DVT may be subjected to unnecessary anticoagulation and its associated risks of bleeding. In contrast, there is a risk of thrombus extension and embolisation when DVT is missed or inappropriately treated.

Keywords: venous thrombosis; thrombophlebitis; risk factors

CPD

Venous thromboembolism (VTE), comprising deep vein thrombosis and pulmonary embolism (PE), is the third commonest vascular disorder in Caucasian populations.[1] In Australia, DVT alone (without concomitant PE) affects 52 persons per 100 000 annually.[2] Timely management of DVT is important as it is a common cause of morbidity. Thromboses of the deep veins in the upper limbs and 'unusual sites', such as mesenteric veins, constitute less than 10% of DVT cases.[2] As they are uncommon, this article focuses only on the risks and diagnosis of lower limb DVT.
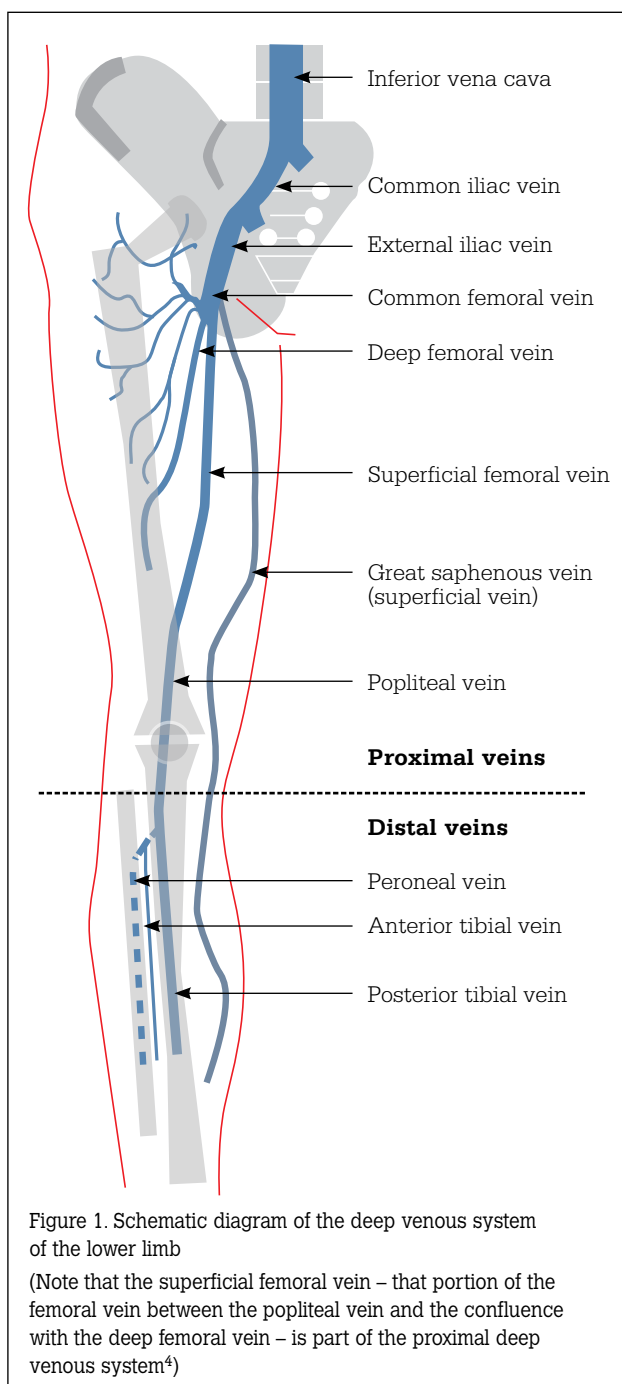
Deep vein thrombosis usually starts in the calf area.[3] Most thrombi confined to the deep veins below the popliteal trifurcation (distal DVT, *Figure 1*) probably resolve spontaneously without causing any symptoms. Distal DVT can extend to the popliteal and femoral veins and other proximal veins. (Note that in some imaging reports, the term 'superficial femoral vein' is applied to that part of the femoral vein between the popliteal vein and the confluence with the deep femoral vein.[4] The superficial femoral vein is therefore a part of the proximal deep venous system.)

Most patients present with symptoms when there is proximal vein involvement. About 50% of patients with untreated symptomatic proximal DVT develop symptomatic PE within 3 months. Despite adequate treatment, DVT can recur. About 10% of patients with symptomatic DVT develop severe post-thrombotic syndrome within 5 years.[3]

Risk factors for VTE

Venous thromboembolism may be provoked by transient and reversible clinical risk factors such as surgery or oestrogen exposure, or long term and permanent factors, such as hemiparesis from stroke (*Table 1*).[5] In 25% of cases, no clinical cause can be ascertained (idiopathic VTE).[6]

About 40–60% of VTE patients in Caucasian cohorts have thrombophilia – a haemostatic disorder resulting in a thrombotic tendency.[7] This may be heritable (eg. factor V Leiden, prothrombin gene mutation and deficiencies of protein C, protein S and antithrombin),[7] or acquired (eg. antiphospholipid antibodies).[8]

Figure 1. Schematic diagram of the deep venous system of the lower limb

(Note that the superficial femoral vein – that portion of the femoral vein between the popliteal vein and the confluence with the deep femoral vein – is part of the proximal deep venous system[4])

Labels on figure:
- Inferior vena cava
- Common iliac vein
- External iliac vein
- Common femoral vein
- Deep femoral vein
- Superficial femoral vein
- Great saphenous vein (superficial vein)
- Popliteal vein

Proximal veins

- -

Distal veins
- Peroneal vein
- Anterior tibial vein
- Posterior tibial vein

The prevalence of thrombophilia varies greatly with ethnicity (*Table 2*).[7,9–13] In Caucasian populations, the most common heritable thrombophilic defects are factor V Leiden and prothrombin gene mutation but these are absent in Indigenous Australians without Caucasian admixture[10] and in east Asians.[9]

Heritable thrombophilia increases the risk of a first VTE[14] but does not appear to be a major determinant of the risk of recurrence (*Table 2*).[13,15–17] In contrast, the antiphospholipid syndrome is a strong risk factor for first and recurrent VTE and warrants consideration of long term anticoagulation.[8,18–20]

Assessment of the patient with suspected DVT

The diagnosis without objective testing is unreliable as many common conditions, such as ruptured Baker cyst, haematoma and venous insufficiency, mimic DVT. In primary care among adults with suggestive symptoms and/or signs, only 29% have ultrasonographically proven DVT.[21]

To better evaluate the clinical probability of DVT before further testing, scoring systems based on symptoms, signs and risk factors have been developed. One such system is the modified Wells score (*Table 3*) which categorises patients as likely to have DVT (score of 2 or more points) or not (<2 points).[22] This score is reproducible and is used together with laboratory and/or imaging studies in a diagnostic algorithm.

Laboratory testing

D-dimer is a degradation product of cross linked fibrin in thrombi. It is elevated in many conditions where fibrin is formed and then degraded, including acute VTE (*Table 4*).[23,24] Various D-dimer assays are now available. They vary in turnaround times and sensitivity and specificity. Enzyme linked immunosorbent assays (ELISAs) are the most sensitive (sensitivity ≥90%) compared with the latex (sensitivity 80–85%) and whole blood (sensitivity ~87%) agglutination assays.[25] The specificity of the various assays differ, but in general, the clinical utility of the D-dimer assays in diagnosing DVT is limited by their low specificity and low positive predictive value (*Table 4*). In contrast, a negative result (normal D-dimer) from a sensitive assay is useful to exclude DVT.

D-dimer levels correlate with the size of the thrombus and clot activity. The sensitivity of an assay may be diminished in cases of

Table 2. Thrombophilia: prevalence and risks of venous thromboembolism				
Thrombophilia	**Prevalence in general population[7,9–11]**	**Prevalence in VTE patients[7,12,13]**	**Odds of first VTE[8,14]**	**Odds of recurrent VTE[13,15–18]**
Factor V Leiden	2.0–4.0% in Australia Absent in Indigenous Australians	10–20%	6.6	1.4
Prothrombin G20210A	2.0–3.2% in Australia Absent in Indigenous Australians	5–6%	2.8	1.2–1.7
Antithrombin deficiency	0.1–0.3%	1–2%	5.0	1.9–2.6
Protein C deficiency	0.2–0.5%	2–3%	6.5	1.4–1.8
Protein S deficiency	0.2–0.5%	2–3%	1.6	1.0–1.4
Lupus anticoagulant	3–6% (depending on assay and cut off values)	6–17% (depending on assay and cut off values)	11.1	2.3–8.5
Anticardiolipin antibodies (aCL)			3.2 (high titre aCL)	

Table 3. Modified Wells score for predicting probability of deep vein thrombosis[22]	
Clinical characteristic[†]	**Score[*]**
Active cancer (treatment ongoing, administered within previous 6 months or palliative)	1
Paralysis, paresis or recent plaster immobilisation of the lower extremities	1
Recently bedridden >3 days or major surgery within previous 12 weeks requiring general or regional anaesthesia	1
Localised tenderness along the distribution of the deep venous system	1
Swelling of entire leg	1
Calf swelling >3 cm larger than asymptomatic side (measured 10 cm below tibial tuberosity)	1
Pitting oedema confined to the symptomatic leg	1
Collateral superficial veins (nonvaricose)	1
Previously documented DVT	1
Alternative diagnosis at least as likely as DVT	–2

* A score of ≥2 indicates that the probability of DVT is likely; a score of <2 indicates that the probability of DVT is unlikely

† In patients who have symptoms in both legs, the more symptomatic leg is used

small, isolated DVT compared with large proximal thrombosis. Further, the passage of time and/or the administration of anticoagulation may slow thrombus turnover thereby reducing assay sensitivity, hence, D-dimer testing may not be useful if a patient has already been effectively treated.[23–26]

Imaging studies

Compression ultrasonography (CUS) is the method of choice to evaluate the lower limbs for DVT.[23,26,27] It is simple, noninvasive and its use has been validated in management studies (*Table 5*). Other methods such as computersied tomography (CT) and magnetic resonance imaging (MRI) are generally limited by availability.[28,29]

Diagnostic algorithm

A patient with symptoms and signs consistent with DVT should be assessed and the clinical (pretest) probability of acute DVT established by using a validated scoring system (*Figure 2*).[22,26,30] Thereafter, if the clinical probability of DVT is low, a D-dimer assay should be performed. In the modified Wells score, a pretest probability less than 2 (DVT unlikely) combined with a normal D-dimer assay result, reliably excludes DVT without the need for imaging studies. If D-dimer is raised, CUS is indicated.

A high pretest probability (DVT likely) should be followed up by CUS. With an abnormal CUS, DVT is diagnosed. However, a normal CUS does not exclude DVT and then a D-dimer assay should be performed. Anticoagulation can be withheld if the D-dimer result is normal. In the event of a raised D-dimer, imaging should be repeated within 1 week (or earlier if symptoms are worsening) as isolated distal DVT that have been missed initially on CUS may extend into the proximal veins and be detected on repeated scanning.[26,30] In patients with unexplained swelling of the entire leg but having negative CUS, the possibility of pelvic vein thrombosis should be considered, in which case, CT, MRI or venography may be indicated.[30]

Figure 2 simplifies the diagnostic process and reduces cost by decreasing the number of patients undergoing both D-dimer testing and imaging studies while allowing room for the clinician to exercise clinical judgment: in the event that confirmatory testing is delayed and the clinical suspicion of DVT remains high, empirical anticoagulation (eg. low molecular weight heparin) should be started if there are no contraindications. Note that this algorithm has been developed and validated for use predominantly in studies of outpatients. The D-dimer assay is frequently positive and has limited usefulness among inpatients (because of comorbidities) and pregnant women.[26,30]

Table 4. Limitations of the D-dimer assay in the evaluation of suspected deep vein thrombosis[23,24]
Clinical situations other than acute VTE resulting in raised D-dimer (potentially diminishing the specificity and positive predictive value of the test)
• Surgery and/or trauma
• Haemorrhage and extensive bruises
• Ischaemic heart disease
• Cerebrovascular accident (stroke)
• Infections
• Malignancy
• Peripheral arterial disease and aneurysms
• Pregnancy
• Advancing age of patients (ie. the very elderly)
• Extensive burns
Clinical situations resulting in a false-negative D-dimer assay
• Small thrombus (eg. isolated distal deep vein thrombosis)
• Time lag between symptom onset and laboratory testing
• Concomitant anticoagulation (with heparin or warfarin)

Table 5. Imaging studies available for the diagnosis of deep vein thrombosis
Compression ultrasonography[27]
• Sensitivity and specificity exceed 95% and 98% respectively for symptomatic proximal DVT
• Sensitivity of 11–100% and specificity of 90–100% for symptomatic distal DVT
• Noninvasive: can be performed relatively rapidly and a portable technique allowing for the bedside assessment of critically ill patients
• Does not visualise the pelvic veins well and cannot be used in obese patients or in patients whose limbs are in plaster casts
Computerised tomography[28]
• Sensitivity and specificity of 96% and 95% respectively in a meta-analysis of studies predominantly examining its use for the diagnosis of proximal DVT
• Can visualise the pelvic veins, define the upper limit of thrombus extension into the iliac veins and inferior vena cava
• Requires the injection of contrast medium, exposes the patient to radiation, may be difficult to interpret when artefact and insufficient venous filling is present, and is more expensive than ultrasonography
• Limited by availability and technical expertise
Magnetic resonance imaging[29]
• Sensitivity and specificity for the diagnosis of symptomatic DVT is 96% and 93% respectively
• Sensitivity for distal DVT is much lower (about 62%)
• Can be performed without the use of contrast medium
• Can visualise the pelvic veins, define the upper limit of thrombus extension into the iliac veins and inferior vena cava
• Limited by availability and technical expertise
Venography (phlebography)[27]
• Reference standard technique
• Reliably detects isolated distal DVT and thrombosis in the iliac veins and inferior vena cava
• Cumbersome to perform, requires the injection of contrast medium, exposes the patient to radiation, may be difficult to interpret when insufficient venous filling is present

In pregnant women, if a DVT is suspected and initial CUS is negative, repeat scanning in 5–7 days is indicated. If pelvic vein thrombosis is suspected, then MRI is the investigation of choice;[31,32] alternatives are pulsed Doppler study of the iliac vein and CT venography.[32]

Further assessment

Evaluation of clinical risk factors for VTE helps determine the duration of anticoagulation.[33] Venous thromboembolism provoked by a transient, reversible cause has a low risk of recurrence and short term anticoagulation is generally required. If the cause is permanent and irreversible (eg. hemiparesis from stroke), or if no provoking factor is identifiable (idiopathic VTE), the risk of recurrence is higher and longer term anticoagulation may be indicated.

Laboratory testing for heritable thrombophilia among unselected patients is generally not indicated as results do not influence patient management.[20,33–35] As long term anticoagulation may be warranted in the antiphospholipid syndrome, testing for lupus anticoagulant and anticardiolipin and anti-β_2 glycoprotein I antibodies should be considered in apparently idiopathic cases or among patients with concomitant connective tissue disorder, previous arterial thromboses (eg. stroke or myocardial infarction) particularly if premature, and/or a history of recurrent pregnancy failure or fetal death.[19,20]

Isolated distal DVT

The risk of symptomatic isolated distal DVT extending into the proximal veins if untreated or inadequately managed varies and ranges from 0–29%.[30] One review estimated that 25% of untreated cases extended proximally within a week.[3]

At diagnosis, up to 40% of cases of symptomatic isolated distal DVT can have coexisting symptomatic PE.[36] Among those with untreated distal DVT, 6.3% developed symptomatic PE within 7 days.[37]

Because of the variable risk of extension and/or embolisation, the optimal management of symptomatic distal DVT is uncertain[38] but some authors suggest that anticoagulation for 6 weeks to 3 months is generally adequate.[39–41]
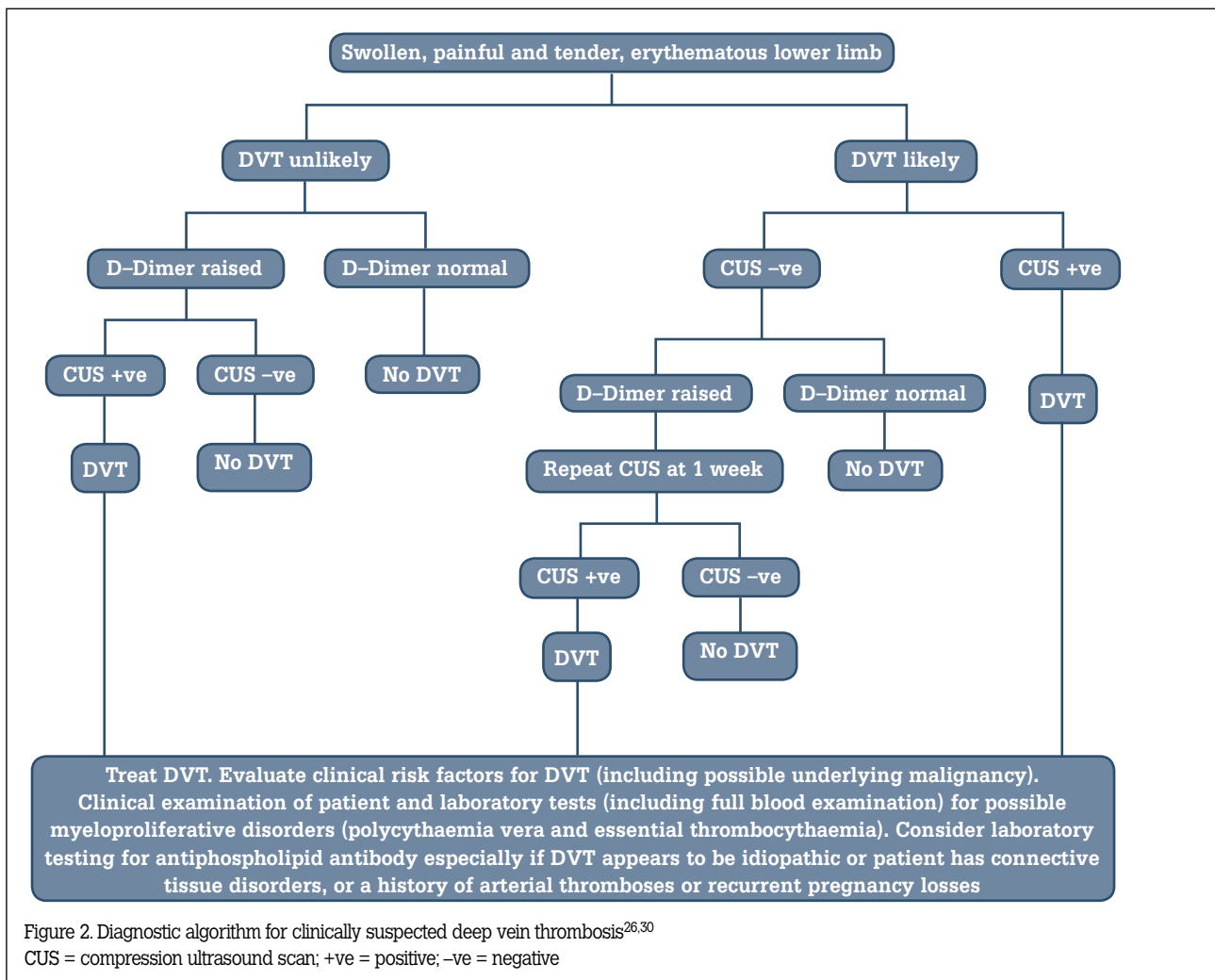
Figure 2. Diagnostic algorithm for clinically suspected deep vein thrombosis[26,30]
CUS = compression ultrasound scan; +ve = positive; –ve = negative

Routine screening of the asymptomatic postoperative patient for DVT is unwarranted.[33] However, if isolated asymptomatic distal DVT is found incidentally, it is reasonable to withhold anticoagulation as many of these thrombi resolve spontaneously and do not cause clinically significant PE.[3,42,43] If anticoagulation is withheld, repeat testing within the next 10 days should be considered to determine if the thrombus has extended.[44] Repeat testing is also indicated if the patient becomes symptomatic.

Superficial vein thrombosis

Concomitant DVT is observed in 2.6–65% of cases of superficial vein thrombosis (SVT) whereas symptomatic PE is present in 0.5–4.0%.[45] In case series involving >15 patients with untreated SVT, DVT and/or PE occurred in 1.7% to >11% within 3 months.[45,46]

Ultrasonography should be performed in cases of SVT to confirm the diagnosis and establish its extent, and to look for the presence of concomitant DVT. Where the proximal extent of SVT is close to the sapheno-femoral or sapheno-popliteal junction, some authors recommend the institution of anticoagulation due to the presumed high risk of DVT and/or PE.[45,46]

Summary of important points

- Diagnostic algorithms incorporating clinical assessment, D-dimer testing and imaging studies have been developed and validated for use in diagnosing DVT.
- Anticoagulation is generally indicated in symptomatic lower limb DVT. This includes thrombosis in the superficial femoral vein, which despite its name, is part of the proximal deep venous system.
- The duration of anticoagulation is largely determined by the site of thrombosis and clinical risk factors; testing for heritable thrombophilia does not generally influence management of the patient and is not warranted.

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