THE NORTHERN HOSPITAL

DEEP VENOUS THROMBOSIS OF THE LOWER LIMB

Jason and Medea, oil on canvas, 1907, John William Waterhouse.

...But he and the heroes quit the throne room, and marvellously amid them all Jason stood out for beauty and grace, and on him the maiden glancing round her bright veil, now gazed in stealthy wonder, pain smouldering in her heart, while like a creeping dream her mind floated after his footsteps as he departed....

...then Argos addressed himself to Jason in these words... "Son of Aison, you'll find fault with what I'm about to say, but in a time of crisis no suggestion should ever be neglected. There is a woman, you have heard me mention her already, skilled in drug magic, taught by Hekate, Perseus' daughter. If we could but win her...

...thus he spoke flattering her, and she with lowered gaze smiles sweet as nectar, and the heart within her melted, she soared on his praise, looked up directly at him...

...First though without hesitation she took from her fragrant breast-band the drug, and he quickly laid his hands on it rejoicing. And indeed she'd have gladly drawn out all the soul from her breast and given it to him, exalting in his great need for her...

Both of them now kept their eyes downcast on the ground out of modesty, now and again stole glances at one another, from beneath bright brows exchanged their smiles of yearning. Finally with great effort, the maiden addressed him thus:

"Listen carefully this is the way I'll work your rescue....

...at dawn, steep this drug in water, strip off naked and rub it all over your body like oil, within it there will be great strength and unlimited prowess - its not men you'd think of matching yourself with, but the immortal gods. On top of this see that your spear and shield are sprinkled, and your sword as well, then you'll be proof against the spear points of the earthborn men, against the irresistible onrush of flame from the deadly bulls.

Yet you will not stay immune for long, but for one day only...

The Argonautika, (Jason and the Argonauts)
3rd Century B.C, Bk III 1684-1716.
Apollonios of Rhodes (c. 305-235 B.C)

Faced with the three deadly tasks of the King of Colchis, in order to gain the Golden Fleece, Jason seeks out the sorceress Medea for help. Medea is in love with Jason and so willingly comes to his assistance with a magical potion that will protect him against the multiple spear thrusts of his enemies. Powerful as this potion is however it will only last for twenty fours hours.

When faced with a patient with possible DVT, we must like Jason seek out the assistance of a magical potion. One option comes us in the form of enoxaparin. Like Medea's magic potion it will in full dosage protect our patient from the multiple "spear thrusts" of pulmonary emboli for a period of twenty four hours.

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Introduction

Ruling out a diagnosis of **deep venous thrombosis (DVT)** is a common presentation to the Emergency department.

This can be problematic as the clinical signs and symptoms cannot definitively make or exclude the diagnosis.

After clinical assessment some cases will clearly need investigation and others will not.

In cases where it is less clear the Wells criteria in conjunction with the d-dimer test can assist in making the decision on whether or not to investigate further.

Above knee DVT carries a much greater risk of pulmonary embolism, than does below knee DVT, (other factors being equal).

The following largely refers to patients who are not pregnant or in the immediate post partum period.

In *general* terms: [2]

For venous thromboembolism (VTE) and **no cancer**, as long-term anticoagulant therapy, the following is currently suggested:

First line therapy:

- DOACs (i.e dabigatran, rivaroxaban, apixaban, or edoxaban) are the preferred method of anticoagulation (in the absence of contraindications to the DOAC)

Second line therapy:

- Vitamin K antagonists (i.e warfarin)

Patients with Cancer:

- For patients with VTE and who also have cancer, LMWH is preferred over DOACs or vitamin K antagonists.

See also separate documents for:

- **DVT in Pregnancy (in Vascular folder)**
- **Iliofemoral DVT (in Vascular folder)**
- **Upper Limb DVT (in Vascular folder)**

- **Malignancy Related Venous Thromboembolism (in Oncology folder)**

Anatomy

For the purposes of the treatment of DVT, the leg veins are divided into "**above knee**" and "**below knee**" deep veins.

Note two important aspects of this definition:

- Although anatomically the **popliteal veins** are "at" the knee, for the purposes of DVT treatment, these are defined as "above" knee veins.

- Radiologists still occasionally report on the "superficial" femoral vein. This can cause confusion, as this is old terminology, for what is now usually termed simply the "femoral vein".

  Historically this vein was considered to be "superficial" only in the sense of it being so, relative to a deeper terminal branch of the common femoral vein (the profunda femoris).

  Anatomically, in addition to the purposes of DVT treatment, the **femoral vein** (old terminology, "superficial" femoral vein) is a **deep** vein.

See also appendix 1 below for the anatomy of the veins of the lower limb.

Pathophysiology

Major Risk Factors for Thromboembolism

1. Immobilization, including:
   - Hospitalization
   - Debility
   - Long haul travel (long international flights)
   - Plaster casts.
   - Limb paralysis
2. Recent surgery.
3. Trauma, especially of lower limbs and pelvis.
4. Intravascular devices, (eg venous cannulas)
5. **Procoagulation conditions**

- e.g. Factor V Leiden, protein S, protein C, elevated homocysteine, etc.

6. Age:

   - The risk increases with age, from 1:10,000 for individuals younger than 40 years to 1:100 for those older than 60 years.

7. **Previous thromboembolism.**

8. Smoking

9. Malignancy

10. Pregnancy and puerperium.

11. Estrogen therapy

13. Chronic medical illness:

    - Including chronic cardiorespiratory disease, IBD and myeloproliferative disease.

Complications:

DVT may be complicated by:

1. Pulmonary embolism

   - PE (symptomatic or asymptomatic):

     ♥ Untreated above knee DVT carries approximately **15-25%** risk of pulmonary embolism and so requires treatment with anticoagulation.

     ♥ Below knee DVT carries a much lower risk of pulmonary embolism (approximately 1% risk of pulmonary embolism in untreated patients).

     Routine anticoagulation in these cases is recommended according to the **level of risk** an individual patient carries, (see below).

2. The post-thrombotic syndrome.

   - The post-thrombotic syndrome occurs in 60 % of patients following DVT.

     This is characterized by pain, swelling and the possible development of pathological changes of venous hypertension, including leg ulceration

3. Recurrent episodes of DVT.

Clinical features

The signs and symptoms of DVT are insensitive and non-specific.

Pain and swelling are commonly seen but their absence is not enough to rule out the condition on clinical grounds.

The most important consideration will be the **clinical setting** and the **risk profile** of the patient for a DVT.

Assessing the Need for an Ultrasound using the Wells Criteria and d-dimer [1]

Table 1. Clinical Model for Predicting the Pretest Probability of Deep-Vein Thrombosis.*

Clinical Characteristic	Score
Active cancer (patient receiving treatment for cancer within the previous 6 mo or currently receiving palliative treatment)	1
Paralysis, paresis, or recent plaster immobilization of the lower extremities	1
Recently bedridden for 3 days or more, or major surgery within the previous 12 wk requiring general or regional anesthesia	1
Localized tenderness along the distribution of the deep venous system	1
Entire leg swollen	1
Calf swelling at least 3 cm larger than that on the asymptomatic side (measured 10 cm below tibial tuberosity)	1
Pitting edema confined to the symptomatic leg	1
Collateral superficial veins (nonvaricose)	1
Previously documented deep-vein thrombosis	1
Alternative diagnosis at least as likely as deep-vein thrombosis	–2

* A score of two or higher indicates that the probability of deep-vein thrombosis is likely; a score of less than two indicates that the probability of deep-vein thrombosis is unlikely. In patients with symptoms in both legs, the more symptomatic leg is used.

The need for an ultrasound can be based on:

1. The clinical pretest probability of a DVT.

AND

2. The D-Dimer level.

The pretest clinical probability of a DVT can be assessed according to the "Wells" criteria: [1] **(see Table above)**

Patients who score 2 or higher on the Wells criteria may have a DVT and should have an ultrasound examination.

A score of less than two makes the diagnosis of DVT unlikely.

The risk of DVT in these patients can then be further assessed by the use of a **D-dimer test**.

There are a number of different D-dimer tests available, with varying degrees of specificity and sensitivity. The Wells study used the "IL" D-dimer test (an automated latex assay, "Instrumental Lab"). The Agen Latex method is not suitable.

IL testing is reported as: mg/L, (Automated IL quantitative assay, and a **level** is quoted)

The Agen test is reported as: mg/L, (Manual Agen semi quantitative assay and a **range** is quoted)

Therefore when requesting the lab to do a d-dimer test for the purpose of ruling out a DVT, the "IL" test should be requested.

If the d-dimer (IL) is negative together with a Well's score of < 2, a DVT is very unlikely and negates the need for an ultrasound.

The patient should be instructed however that should there be any change in symptoms they will need to be reassessed.

Note that this scoring system does not take into consideration the risk factors of pregnancy and the puerperium.

If the US is negative, yet there is *moderate to high clinical risk and a positive d-dimer* has been found, then further imaging, (especially to rule out iliac, pelvic or IVC thrombosis) should be considered.

Alternatively a repeat US within one week, (or before if further symptoms develop), may be considered.

Where there is extensive proximal DVT there may be signs that the circulation to the limb is compromised:

- The whole limb is swollen.
- Evidence of venous congestion.

Investigations

Blood tests:

1. FBE

2. U&Es/glucose

3. Procoagulant screen, (in particular for an unprovoked DVT):

    - **Antiphospholipid antibodies should be checked in all patients.**

        - ♥ The Antiphospholipid antibodies include:

            - ♥♥ Lupus anticoagulant, anti-cardiolipin antibodies and B2-glycoprotein antibodies.

            Note that Antiphospholipid antibodies syndrome is usually an *acquired* condition, and will require long term therapy following a first unprovoked DVT.

    - Further testing will then depend on the **age group:**

        - ♥ **Above 45 years old**: Routine thrombophillia screen should NOT be done.

        - ♥ **Below 45 years old**: Thrombophillia screen should be performed:

            Thrombophillia screen includes:

            - ♥♥ Factor V Leiden
            - ♥♥ Prothrombin Gene Mutation
            - ♥♥ Protein S
            - ♥♥ Protein C
            - ♥♥ Anti-thrombin III

    Thrombophillia screen should be done **prior** to the commencement of anticoagulation as it may affect results.

4. D-dimers:

    D-dimers should be used in conjunction with the Wells risk stratification score, (as above)

Note that D-dimers can be falsely negative and falsely positive.

Other conditions which may elevate the d-dimer level include:

- Malignancy
- Infection
- Recent surgery
- Trauma.
- Pregnancy.

Ultrasound:

In New Zealand and Australia, **compression ultrasound (CUS)** is the standard diagnostic test for investigation of suspected DVT.

Ultrasound of **the whole leg** is carried out, looking for proximal *and* distal DVT.

If strong clinical suspicion remains despite a negative CUS, CT venography or magnetic resonance direct thrombus imaging (MRDI) or repeat CUS should be considered.

CT Venography or MRI may be used to exclude proximal DVT of the iliac or other pelvic veins.

MRI:

Magnetic resonance venography (MRV) is more sensitive and more specific than ultrasound in the detection of deep venous thrombosis and may be useful when ultrasound examination is equivocal or when strong clinical suspicion remains despite a normal ultrasound examination.

It has the added advantage over ultrasound in being able to detect thrombosis within the lilac, pelvic veins or the IVC and can detect alternate or associated pathology in the limb, pelvis or abdomen.

CT Venogram:

This may be considered in the following cases:

- Unavailability of US.
- Patients with negative US with unexplained swelling of the entire lower limb, (isolated iliac vein thrombosis may be missed on US)

- It may also have a role in distinguishing acute recurrent DVT from chronic thrombus as ultrasound cannot reliably distinguish between old and new thrombus.

- In cases of equivocal or inconclusive ultrasound results.

CT screening for **occult malignancy:**

- Routine CT imaging for underlying malignancy is not recommended, however it should be considered in **high risk** patients (e.g. elderly patients, presence of constitutional symptoms, strong family history).

  In this regard routine aged and sex based malignancy screen (e.g. mammograms and PAP smears) should also be considered.

Management

Above knee DVT versus below knee DVT:

The approach to treatment may differ between DVT above the knee and DVT below the knee.

Heparin and warfarin therapy is currently the most common anticoagulant treatment.

There remains some controversy but in general most current expert opinion holds that:

For above knee DVTs:

- All cases should be treated with full anticoagulation, (this includes both symptomatic and asymptomatic cases).

For below knee DVTs:

- If the patient is **symptomatic**, (pain and swelling) then anticoagulation should be undertaken, (minimum 3 months).

- If the patient is **asymptomatic** (i.e. an incidental finding) AND **has no other high risk factors** then it is not necessary to anticoagulant (**but close follow-up with repeat ultrasound examinations will still be mandatory**).

  Although not of current proven benefit it is reasonable, to treat these patients with **daily aspirin.**

- If the patient is asymptomatic, but has **high risk features**, then anticoagulation should be undertaken.

  Important high-risk factors include:

- ♥ Close proximity to the knee crease (within 1 cm of the knee crease)
- ♥ Known positive thrombophilia screen
- ♥ Previous history of thrombosis.
- ♥ Active malignancy
- ♥ Clinician concern
- ♥ Follow-up leg US is not feasible.

If there is subsequent clot extension on US examination, then anticoagulation will need to be commenced.

A follow up US is recommended over a period of 2 weeks following diagnosis, (e.g. at 5 and 10 days)

If clot *extension* is detected, anticoagulation for is recommended.

Anticoagulation:

In *general* terms: [2]

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Second line therapy:

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For patients with VTE and who also have cancer, LMWH is preferred over DOACs or vitamin K antagonists.

Patients with Cancer:

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For Rivaroxaban Therapy:

Initial treatment of DVT: **15 mg b.d for a period of 3 weeks.**

Then:

Maintenance treatment of DVT: **20 mg daily.**

For prevention of recurrent DVT: **20 mg daily.**

Rivaroxaban is currently the preferred DOAC treatment

For Dabigatran Therapy:

Initial **parenteral** anticoagulation is given before dabigatran (and edoxaban), but is not given before rivaroxaban and apixaban.

For VTE, treat with a parenteral anticoagulant for at least 5 days before starting dabigatran.

Continue dabigatran for at least 3 months.

Adult, 150 mg twice daily.

Increased risk of major bleeding or > 75 years, *Adult,* 110 mg twice daily.

Note that the reason for 5 days of initial enoxaparin is because that was the way the initial trials were designed and FDA approval was given on that basis. Also it is important to note that Dabigatran is not indicated on PBS in Australia for the treatment of DVT and PE (unless the patient has concurrent AF).

Rivaroxaban is currently the preferred treatment.

For Apixaban Therapy:

- *Adult,* 10 mg twice daily for 7 days, then 5 mg twice daily for at least 6 months.

Prevention of subsequent VTE:

- *Adult,* 2.5 mg twice daily.

For Enoxaparin and Warfarin Therapy:

1. Enoxaparin, (clexane):

    - 1.5 mg/kg SC, daily (maximum dose 150 mg daily)

    Or:

    - 1 mg/kg SC, twice daily (maximum dose 100 mg twice daily).

    Note that LMWH requires monitoring and possible dose adjustment in the presence of *renal impairment* (calculated creatinine clearance $\leq$ 30 mL/min).

This is continued until warfarin is therapeutic, (and a minimum period of 48 hours).

See latest Therapeutic Guidelines for full prescribing details.

2. Warfarin is commenced as soon as the diagnosis is made.

   - A starting dose of **5 mg** is given.
   - A therapeutic range of 2 - 3 INR is generally aimed for, but this can vary according to the exact indication for anticoagulation.
   - Warfarin is absolutely contraindicated in pregnancy, but is safe in breast feeding.

   See latest Therapeutic Guidelines for full prescribing details.

Full anticoagulation will:

- Reduce the risk of potentially lethal PE.
- Reduce the longer term local complications of DVT, such as *chronic venous insufficiency and recurrence of DVT*.

Duration of therapy is generally for a minimum of **3 months**, but may be longer, in some situations or even life-long for certain underlying procoagulation disorders.

The exact duration of treatment in complex cases is best determined by a Clinical Hematologist.

Role of Aspirin:

Aspirin may be considered for extended treatment of VTE

In patients with an unprovoked proximal DVT or PE who are stopping anticoagulant therapy and do not have a contraindication to aspirin, is an option for ongoing prevention of recurrent VTE

Thrombolysis & Mechanical Clot Removal:

Thrombolysis is not generally considered for lower limb DVTs unless there are special circumstances such as cases of limb-threatening *massive iliofemoral vein thrombosis*.

Mechanical clot removal is an alternative if there is a strong contraindication to thrombolysis.

IVC filter:

Insertion of a **temporary** IVC filter may be required for above knee DVTs in cases where:

- Therapeutic anticoagulation is contraindicated because of a high risk of bleeding,
- Who have objectively confirmed recurrent VTE despite therapeutic anticoagulation.

IVC filters are generally not recommended for cases of below knee DVT.

Haematology should be involved in this decision.

Compression stockings:

Post-thrombotic syndrome (PTS) is characterised by symptoms of leg, itching, cramps and pain, with physical signs of leg oedema, hyperpigmentation, new venous ectasia and, rarely, in its most severe manifestation, by the presence of a venous stasis ulcer.

Around 15-50% of patients who have suffered with DVT will develop PTS.

Routine use of graduated compression stockings is **no longer** recommended.

Disposition

Most DVTs requiring anticoagulation can be managed as outpatients

Patients presenting out of hours:

Patients are frequently referred by GPs "out of hours" with a *provisional* diagnosis of DVT.

If there is reasonable likelihood the patient has a DVT then they may be treated with a stat dose of clexane and sent home (or admitted to the SSU, depending on the patient) with an ultrasound organized for the following morning.

Admission to Hospital:

Indications for admission include:

- The patient is not suitable for outpatient management
- The patient has significant complicating medical or social co-morbidities.
- Patients with very extensive DVT or DVT that involves iliac vessels, or femoral vessels to the femoral ring.

Vascular referral:

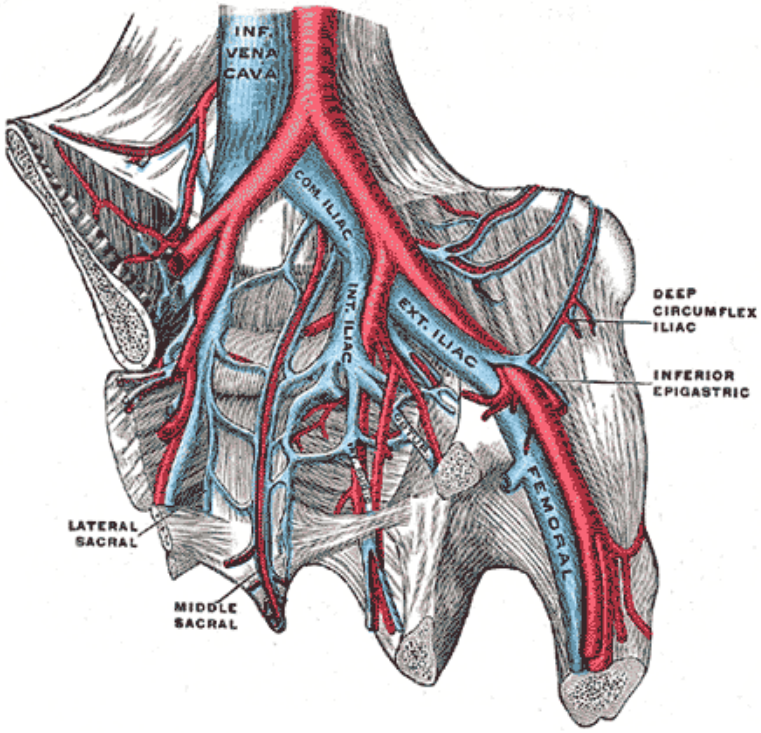
- In very extensive cases of massive ilio-femoral thrombosis there is not only high risk of embolism but also of ischemic venous infarction of the limb.

  These cases should be referred to the vascular unit for consideration of thrombolytic therapy or surgical evacuation of clot.

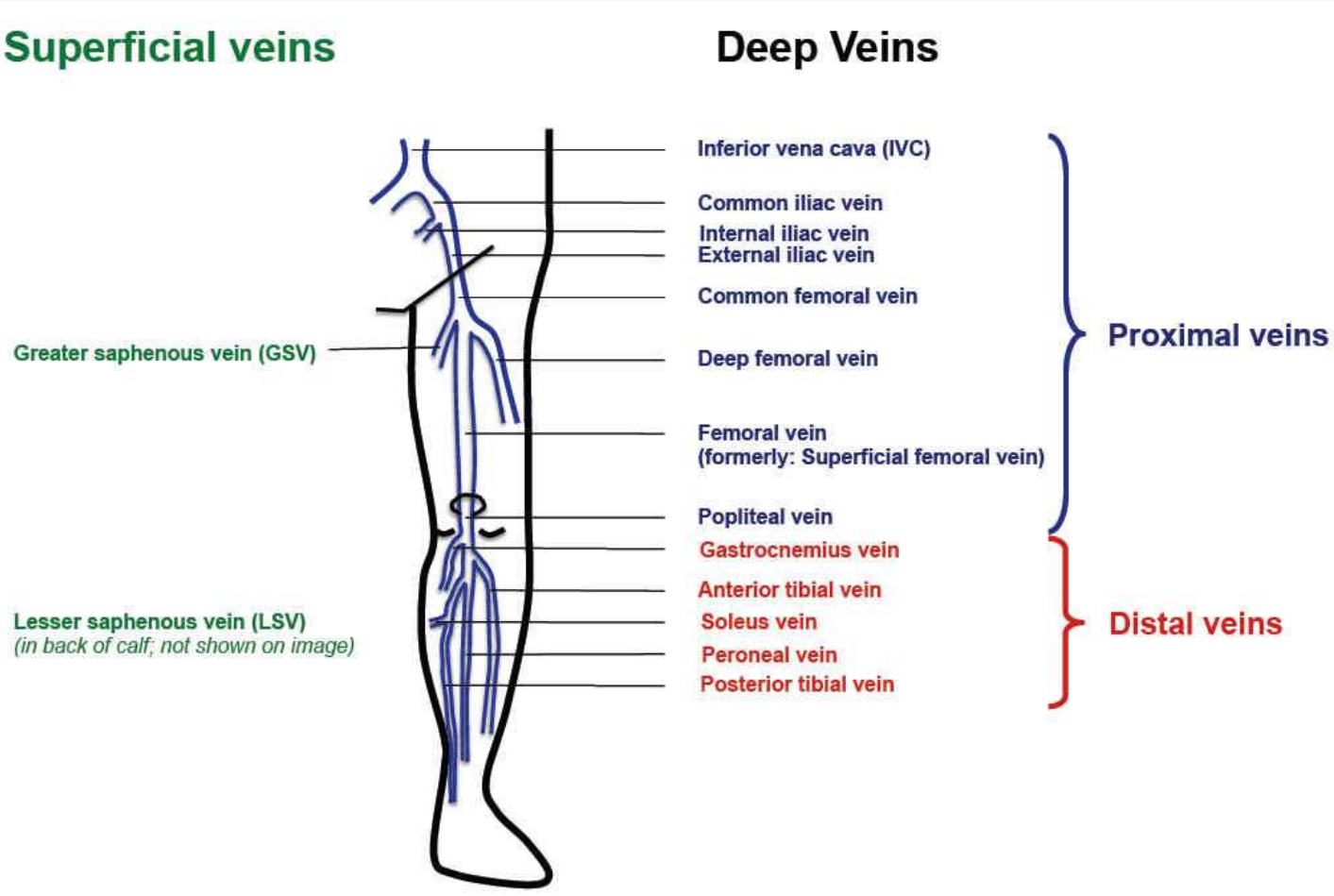
Hematologists:

All patients with VTE are now generally referred to a **Hematology Unit** in order to determine the most suitable anticoagulation regime.

Appendix 1: *The Deep Veins of the pelvis and lower limb:*



Left: The deep veins of the pelvis, (Gray's Anatomy, 1918)



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1. Wells PS, Anderson DR et al, Evaluation of D-Dimer in the Diagnosis of Suspected Deep Vein Thrombosis. NEJM, 349:13, September 25 2003, p.1227-1235.

2. Clive Kearon, at al. Antithrombotic Therapy for VTE Disease CHEST Guideline and Expert Panel Report. CHEST 2016; 149 (2): 315-352.

3. eTG - November 2018.

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