Phlebothrombosis is a very common and very serious condition. Blood clots in veins can mobilize and cause significant harm and even death in some cases by blocking downstream vessels. This condition needs to be thought of in all new hospital admissions, especially those who will be particularly immobile or those undergoing operations, so they can be given medical prophylaxis to reduce the chance of a blood clot forming in the venous system.

Definition and Background of Phlebothrombosis and DVT

Phlebothrombosis occurs when a blood clot forms in a vein that is not inflamed. When a blood clot forms in the presence of inflammation, this is called thrombophlebitis.
As the majority of these blood clots occur in the deep veins of the calf, we will focus on DVTs (deep vein thrombosis). DVTs are a very serious problem in patients and many protocols has been put in place to try and reduce the number of DVTs that occur. The main complication that worries healthcare professionals is VTE (venous thromboembolism). A VTE is when a DVT leads to a pulmonary embolism (PE); this occurs when a blood clot from the deep veins of the calf breaks off (embolizes) and travels towards the heart and into the pulmonary vasculature.

The embolus reaches the inferior vena cava and enters the right atrium where it passes into the right ventricle and into the pulmonary arteries. Depending on the size of the clot, it can block anywhere from the pulmonary arteries to the pulmonary capillary bed; the larger the clot, the more severe its effect. Serious VTEs can cause sudden death by obstructing the main pulmonary artery, preventing blood flow to the lungs and therefore the body.

Epidemiology of Phlebothrombosis and DVT

Occurrence of phlebothrombosis and DVT

1 in 1000 adults per year suffers from DVT. It is rare in children and hardly ever leads to VTE. DVT is a disease of aging as it is much more common in the elderly compared to younger adults. It occurs at a rate of 1/10,000 for people under 40 and increases to 5.5/1,000 at the age of 80. There is an increase in the age group of women of childbearing age as VTE is a known complication of pregnancy (0.001%).
VTE is much more common in those who undergo orthopedic operations as recovery usually involves immobilization; nearly all who undergo such procedures are now given prophylaxis (heparin) to try and prevent this. It is unknown why, but Caucasians have a higher VTE risk than Asians.

Genetic conditions can lead to thrombophilia which increases the chance of DVT formation. Different conditions are more common in different parts of the world and this therefore affects the incidence of DVT; e.g. Factor V leiden. DVT occurs in 25 – 50% of surgical patients.

Etiology of Phlebothrombosis and DVT

Causes of phlebothrombosis and DVT

Virchow’s triad divides most of the causes of DVT into three categories:

- Hypercoagulability
- Venous stasis
- Endothelial changes (blood vessel lining)

This does not cover immune system activation, oxygen concentration or platelet activation.

Risk Factors

Patients with the following characteristics are at a greater risk for phlebothrombosis and DVT:

- **Older age**: DVT is a disease of aging
- **Synthetic estrogen (contraceptive pill)**: because it makes the blood hypercoagulable
- **Trauma**: causes damage to the endothelial lining of the vein
- **Major surgery** (especially orthopedic): can cause trauma to vein endothelium and/or increases immobility which can lead to venous stasis
- **Previous DVT/VTE**: risk of developing another is increased
- **Obesity**: more likely to be immobile and have venous stasis
- **Immobility** (e.g. long flight): causes venous stasis
- **Thrombophilia**: many genetic conditions are responsible for making the blood
hypercoagulable. e.g. deficiency of certain proteins that inhibit excess clotting, or excess of proteins that promote clotting.

Others: intravenous drug use, HIV, infection, cancer, chemotherapy, pregnancy and the postpartum period, Hughes syndrome (or antiphospholipid syndrome, an autoimmune disease in which an overactive immune system produces antiphospholipid antibodies (aPL) which cause the blood to clot too quickly both in veins and arteries), dehydration, smoking.

Pregnancy, pseudo-pregnancy (oral contraceptives) and post-menopausal medication increase production of clotting factors by the liver. Also, cigarette smoking adds to the risk for clot formation.

Pathophysiology of DVT

DVTs form when the clotting cascade is activated inappropriately. Virchow’s triad states that there are three main scenarios where this occurs:

- Venous stasis
- Hypercoagulability
- Endothelial damage

DVTs most commonly form in the deep veins of the calf. The veins affected the most include the femoral, popliteal and iliofemoral veins. Proximal DVTs are more likely to cause a PE and are generally considered more serious. DVTs can also form in the veins of the pelvis. DVT commonly starts to form in the venous valves; the nature of the blood flow causes this area to be hypoxic. This along with venous stasis, can activate certain clotting factors such as the hypoxia-inducible factor-1. Clots consist of red and white blood cells, platelets and fibrin. Once a DVT has formed, it may cause more clots to form as it can induce inflammation.

The calf muscles are responsible for squeezing the veins in the leg and therefore maintain venous flow. Patients who are immobile (bedridden, undergoing an operation, etc.) and do not walk for a long amount of time do not use their calf muscles frequently and therefore are at higher risk of developing a DVT due to venous stasis.
Endothelial damage causes the formation of a DVT. This is because the coagulation cascade becomes activated once the clotting proteins in the blood are exposed to tissue factor (in damaged endothelial cells), which cleaves prothrombin into thrombin. This damage can occur as a result of vasculitis, trauma (intravenous drug users) or from medications such as chemotherapy.
Some conditions can increase the risk of DVT by making the blood more coagulable. Such conditions include nephrotic syndrome and antiphospholipid syndrome. Some of these conditions are genetic and run in families; these include thrombophilia and factor V leiden mutations. Blood can become hypercoagulable for other reasons such as increased amount of exogenous oestrogen from hormonal replacement therapy or from the combined oral contraceptive pill. DVT is most common in hospital patients (especially those undergoing orthopedic or major operations) and may occur on long flights in people with low-risk of developing a DVT (such as tennis player Serena Williams).

Two main complications can result from DVT; these are PE and post-thrombotic syndrome (see ‘Complications’ below). Pulmonary embolism causes damage by obstructing pulmonary arteries and causing ventilation perfusion mismatch and cardiac strain; depending on the size and what artery has been blocked, the patient can present with shortness of breath or they can suddenly collapse and die.

Signs and Symptoms of Phlebothrombosis and DVT

Recognizing phlebothrombosis and DVT

DVTs most commonly affect the calf and patients typically present with the following;

**UNILATERAL:**

- Increase in calf temperature
- Tenderness
- Erythema (redness)
- Swelling
- Pitting edema (venous stasis)
- Fever

Pulmonary embolus presents in various ways depending on what artery has been obstructed:
- 40% have a silent PE
- Chest/upper back pain – usually worse on inspiration
- Coughing – haemoptysis may be present
- Shortness of breath
- Dizziness
- Syncope

As differential diagnoses, ruptured Baker’s cyst and cellulitis should be considered.

Diagnosis and Investigations of Phlebothrombosis and DVT

Methods of detecting phlebothrombosis and DVT

Clinical examination along with a detailed history can raise suspicion of DVT. A positive D-dimer test is a quick screen that can rule out DVT most of the time if it is negative. The patient should then undergo imaging, usually ultrasound, to confirm DVT. Scoring systems are sometimes used to estimate the probability of DVT and to determine which test is to be performed; e.g. Wells score. The following list comprises possible investigations:

**D-Dimer**

- This is a blood test that can rule out DVT when it is negative.
- However, when this test is positive, it does not confirm DVT as it can be raised for many other reasons (infection, cancer, pregnancy, post-operatively).
- D-dimer is therefore sensitive but not specific for DVT.
- If there is clinical suspicion along with a positive D-dimer, the patient should undergo an ultrasound of the lower extremities.
- D-dimers are fibrin degradation products. Plasmin dissolves a clot causing increased levels of D-dimers, but infection, surgery, pregnancy, cancer and many more also raise D-dimer blood levels.

**Imaging**

- Ultrasound: US is a quick and easy test which can quickly detect DVT; a proximal compression ultrasound or a whole-leg ultrasound may be performed.
- Doppler ultrasound, MRI venography, CT scan venography or MRI of the thrombus.
- Contrast venography is the gold standard test for confirming DVT, however, it is rarely used due to invasiveness and cost.

**Clinical examination**

- As discussed above, one of the patient’s calves may be warm, red, swollen and
painful.
- Pitting edema may be demonstrable.

**Detailed history**

- To assess the risk of DVT, a detailed history is essential. Certain risk factors may make you more suspicious of DVT (e.g. a patient with cancer who has just been on a long flight).
- Blood tests - the patient may have elevated D-dimer, ESR (erythrocyte sedimentation rate) and WBC (white blood cell) count.

**Note:** OSCE examinations commonly provide histories of patients with multiple risk factors of DVT such as recent immobility.

**Wells scoring system**

1. Active cancer (treatment in last 6 months or palliative) +1
2. Calf swelling more than 3 cm compared to asymptomatic calf (measured 10 cm below tibial tuberosity) +1
3. Swollen unilateral superficial veins in symptomatic leg (non-varicose) +1
4. Unilateral pitting oedema in symptomatic leg +1
5. Previous documented DVT +1
6. Swelling of entire leg +1
7. Local tenderness along deep venous system +1
8. Paralysis, paresis or recent cast immobilisation of lower extremities +1
9. Bedridden for more than 3 days, or major surgery required anesthetic in the past 12 weeks +1
10. Alternative diagnosis at least as likely -2

The results are classified as follows:

- 3 - very likely - 53 %
- 2/1 - moderate likelihood - 17 %
- 0 - unlikely - 5 %
- A score of 2 or more is generally considered significant.

**Classification of DVT**

**Types of DVT**

DVT is categorized according to the following types:

- **Provoked DVT** - DVT associated with acquired risk factors
- **Unprovoked DVT** - DVT not associated with acquired states
- **Acute DVT** - pain and swelling, usually due to the occlusive nature of the clot
- **Chronic DVT** - symptoms lasting more than 10 days
- **Asymptomatic DVT** - found incidentally and causes no symptoms
- **Proximal DVT** - occurring above the knee
- **Distal DVT** - occurring below the knee

**Treatment and Prevention of Phlebothrombosis**
and DVT

The following treatments are recommended:

**Anticoagulation**

- Does not directly treat the clot but prevents further clots from forming
- Standard treatment duration is 3 months
- Treatment may be extended in high risk cases or where no cause can be found

**LMWH**

Low molecular weight **heparin** (enoxaparin 1.5 mg/kg/24 h subcutaneous) or **fondaparinux**. It is now preferred over unfractionated heparin; no monitoring, fewer doses, fewer long term side effects and has less effect on thrombin but the same effect on factor Xa.

LMWH inhibits coagulation by selectively inhibiting factor Xa via anti-thrombin (reducing the amount of thrombin that forms from prothrombin). It only has a weak effect on thrombin itself.

Monitored by anti-factor Xa assay which measures the activity of anti-factor Xa.

There are many contraindications to **anticoagulation**. **Anticoagulative therapy** should only be started once the patient has been evaluated for risks of excessive bleeding, other conditions that could constitute a contraindication and interactions with other medications.

Cancer patients require heparin for 6 months and then they need to be re-evaluated. LMWH is given to the majority of patients undergoing surgery and to patients at risk of developing DVT during their hospital stay.

![Warfarin](https://example.com/warfarin.jpg)

*Image: “Warfarin tablets” by Gonegonegone. License: CC BY-SA 3.0*
- Warfarin is a vitamin K antagonist, which inhibits clotting factors that require vitamin K for their synthesis in the liver. These clotting factors are X, IX, VII, II.

**Note:** The inhibited clotting factors can be remembered simply by memorizing the year 1972 (10, 9, 7, 2).

- Warfarin should be started at the same time as LMWH as it is prothrombotic for the first 2 days of treatment.
- Warfarin is a long-term medication, which is used in patients where there is expected recurrence/high-risk of another DVT. Treatment can last months or years depending on the cause.
- When INR is 2-3, the patient can be taken off LMWH.
- Patients who have experienced a DVT post-operatively should stay on warfarin for 3 months.
- Those who experience a DVT where no cause can be found should stay on warfarin for 6 months.
- **Recurrent DVT or thrombophilia patients should remain on warfarin for life.**
- As with all anticoagulation medications, there are many contraindications. Caution should be taken when prescribing warfarin in patients who have a high risk of falls (e.g. the elderly), as they will be at higher risk of a serious bleed.
- Warfarin should not be used for VTE prevention in pregnancy.

**Inferior vena cava filters**

- These filters are implanted into the IVC below the origin of the renal veins and act as a barrier, preventing clots from spreading into the heart and pulmonary arteries, hence, preventing PE.
- They are effective where anticoagulation fails.
- They are only recommended in high-risk patients.

**Thrombolysis**

- An enzyme is given intravenously and breaks up clots. This reduces the chance of damage to venous valves in the leg.
- Reduced the chance of developing post-thrombotic syndrome by a third.
- Risk of major bleeding.

**Graduated Compression stockings**

- These stockings compress the legs of patients and can reduce venous stasis.
- They can help prevent long-term complications of DVT such as development of ulcers, **skin changes**, pain and swelling.
- Useful in prevention of further DVTs.
- Should never be used in patients who suffer from **ischaemia** as it can worsen this condition, causing **necrosis** and **gangrene**.

**Intermittent pneumatic compression devices**

- A sleeve is placed around the leg and is inflated with air. This compresses the patient’s leg and can help with conditions such as venous stasis.
- This can reduce the risk of DVT by up to 66 % in surgical patients.

**Mobility**

- Patients should be encouraged to get out of bed and walk early after an operation to increase the muscular pump and venous flow in their legs.
Prevention
- Anticoagulants at post partum and early ambulation
- Anti-embolism stockings
- Pneumatic compression device to enhance blood flow
- Venous emptying
- Elevation of leg 15-20 degree prevents stasis
- Gradual ambulation with elastic support

Complications of DVT

Risks inherent in phlebothrombosis and DVT
As discussed above, the most serious complication of DVT is PE. This can lead to minor respiratory distress or sudden death. The outcome depends on the size and number of clots.

Post-thrombotic syndrome is the commonest complication of proximal DVTs. Symptoms consists of pain and swelling. Leg ulcers may develop in the long-term and mobility can be reduced. In some cases, patients complain of paraesthesia. PTS occurs in 25 – 50 % of patients and 7.5 % of these patients develop severe PTS.

Review Questions
The correct answers are below the references.

1. A man experiences a DVT and goes to his Doctor. After many investigations, they cannot determine the reason why he has a DVT. How long should this man stay on warfarin for?
   A. 2 weeks
   B. 1 month
   C. 3 months
   D. 5 months
   E. 6 months

2. How does the anticoagulant drug warfarin work?
   A. Inhibits factor Xa
   B. Increases the amount of factor IX
   C. Antagonises vitamin K inhibiting the production of factors II, VII, IX and X
   D. Antagonises vitamin C inhibiting the production of factors II, V and X
   E. Acts as an enzyme and breaks down fibrin clots by fibrinolysis

3. What is the most common complication after a proximal DVT?
   A. Pulmonary embolism
   B. Post-thrombotic syndrome
   C. Osteoarthritis
   D. Factor V leiden mutation
   E. Cerebrovascular accident
References


Oxford Handbook of Clinical Medicine 8E


Correct answers: 1E, 2C, 3B

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