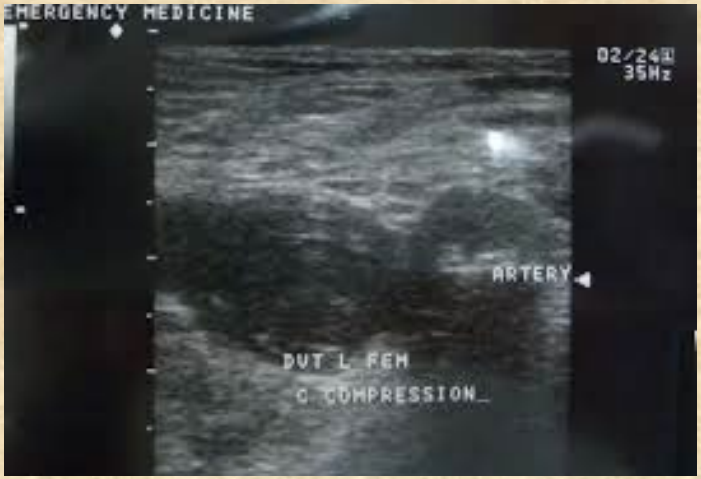
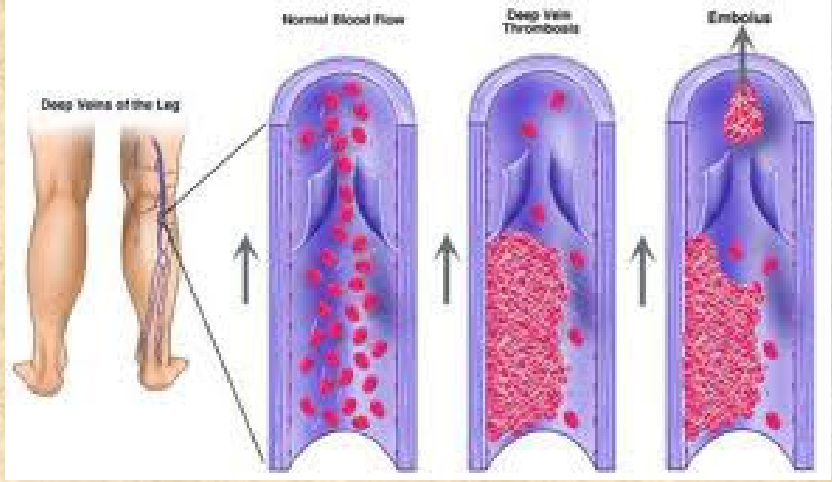




Thrombotic disorders

Dr.Mousa Qasim Hussein
Professor internal medicine

Venous thromboembolic disease (venous thromboembolism)

While the most common presentations of venous thromboembolism (VTE) are deep vein thrombosis (DVT) of the leg and or pulmonary embolism, similar management principles apply to rarer manifestations such as jugular vein thrombosis, upper limb DVT, cerebral sinus thrombosis and intra-abdominal venous thrombosis (e.g. Budd–Chiari syndrome).

VTE has an annual incidence of approximately 1 : 1000 in Western populations.
The relative incidence of DVT:PE is approximately 2 : 1.
Mortality 30 days after DVT is approximately 10%, compared to 15% for PE.
All forms of VTE are increasingly common with age and many of the deaths are related to coexisting medical conditions, such as active cancer or inflammatory disease, which predispose the patient to thrombosis in the first place.

Venous thrombosis

May arise either because of :

1. **Damage to, or pressure on veins (e.g. varicos veins or pelvic tumour), or:**
2. **As a result of changes in the plasma or cellular elements of the blood.**

Factors predisposing to venous thrombosis

1-Patient factors

- Increasing age
- Obesity
- Varicose veins
- Previous deep vein thrombosis
- Family history, especially of unprovoked venous thromboembolism when young
- Transient additional risk factors:

Pregnancy/puerperium
Oestrogen-containing oral contraceptives and hormone replacement therapy
Immobility, e.g. long-distance travel (> 4 hrs)
Intravenous drug use involving the femoral vein
Surgery
Medical illnesses

2-Surgical conditions

- Major surgery, especially if > 30 mins' duration
- Abdominal or pelvic surgery, especially for cancer
- Major lower limb orthopaedic surgery, e.g. joint replacement and hip fracture surgery

3-Medical conditions

- Myocardial infarction/heart failure
- Inflammatory bowel disease
- Malignancy (anti-cancer chemotherapy increases the risk of venous thromboembolism compared with cancer alone)
- Nephrotic syndrome
- Chronic obstructive pulmonary disease
- Pneumonia
- Neurological conditions associated with immobility, e.g. stroke,
paraplegia, Guillain–Barré syndrome
- Any high-dependency admission

4-Haematological disorders

- Polycythaemia rubra vera
- Essential thrombocythaemia
- Deficiency of natural anticoagulants: antithrombin, protein C, protein S
- Paroxysmal nocturnal haemoglobinuria
- Gain-of-function prothrombotic mutations: factor V Leiden, prothrombin gene *G20210A*
- Myelofibrosis

5-Antiphospholipid syndrome

Unilateral leg swelling

Most leg swelling is caused by oedema, the accumulation of fluid within the interstitial space. There are three explanatory mechanisms for development of oedema include:

1 -increased hydrostatic pressure in the venous system due to increased intravascular volume or venous obstruction

2- decreased oncotic pressure secondary to a decrease in the plasma proteins that retain fluid within the circulation

3-obstruction to lymphatic drainage (‘lymphoedema’).

May occur in isolation or combination.

Presentation

Any patient who presents with unilateral leg swelling should be assessed with the possibility of deep vein thrombosis (DVT) in mind.

1-The pain and swelling of a DVT is often fairly gradual in onset, over hours or even days.

2-Sudden-onset pain in the posterior aspect of the leg is more consistent with gastrocnemius muscle tear (which may be traumatic or spontaneous) or a ruptured Baker's cyst.

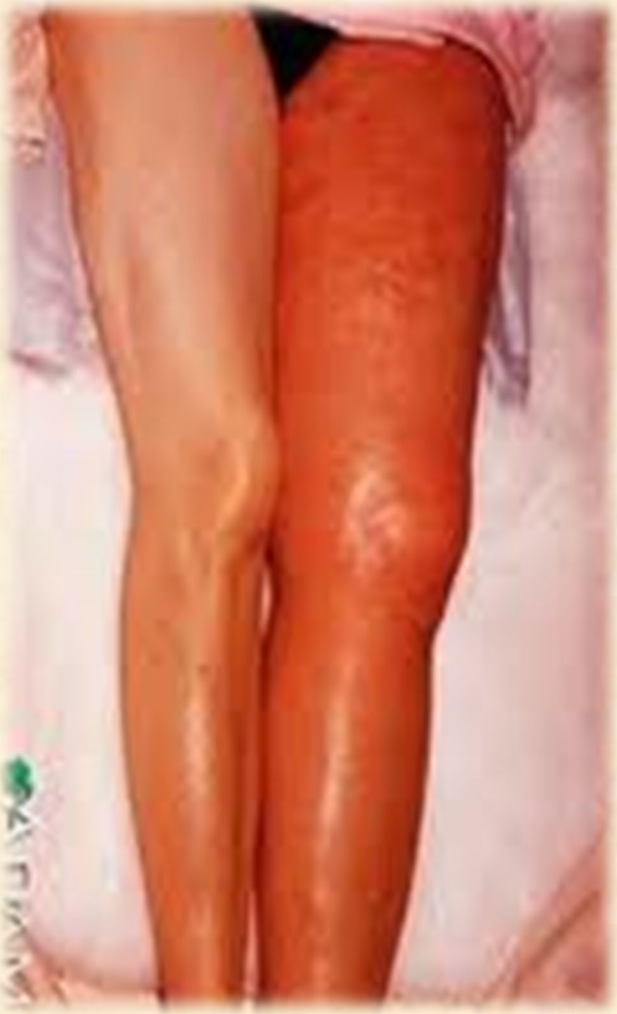
3-Leg swelling and pain associated with paraesthesia or paresis, or in the context of lower limb injury or reduced conscious level, should always prompt concern regarding the possibility of compartment syndrome .

4-Cellulitis is usually characterised by erythema and skin warmth localized to a well-demarcated area of the leg and may be associated with an obvious source of entry of infection (e.g. leg ulcer or insect bite).

The patient may be febrile and systemically unwell. Superficial thrombophlebitis is more localised; erythema and tenderness occur along the course of a firm, palpable vein.

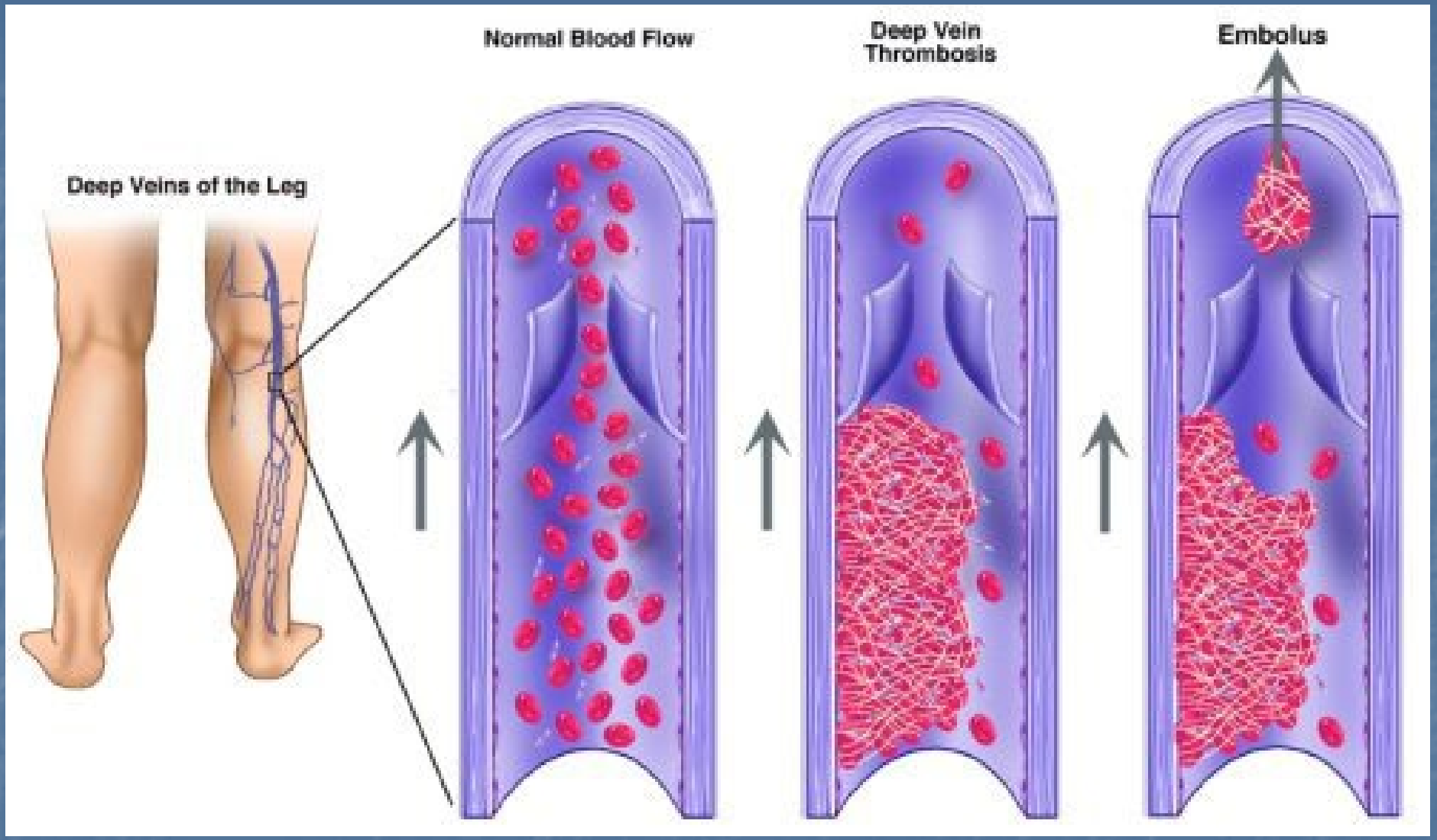
Clinical assessment

Lower limb DVT characteristically starts in the distal veins, causing:
Pain, swelling, increase in temperature and dilatation of the superficial veins.
Often, however, there are only minimal symptoms and signs.
It is typically:
unilateral but may be bilateral when clot extends proximally into inferior vena cava.
Bilateral DVT is more commonly seen in patients with underlying malignancy or anomalies of the inferior vena cava.



Examination of any patient presenting with leg swelling should include assessment for malignancy (evidence of weight loss, a palpable mass or lymphadenopathy). Malignancy is a risk factor for DVT, but pelvic or lower abdominal masses can also produce leg swelling by compressing the pelvic veins or lymphatics. Early lymphoedema is indistinguishable from other causes of oedema. More chronic lymphoedema is firm and non-pitting, often with thickening of the overlying skin, which may develop a ‘cobblestone’ appearance

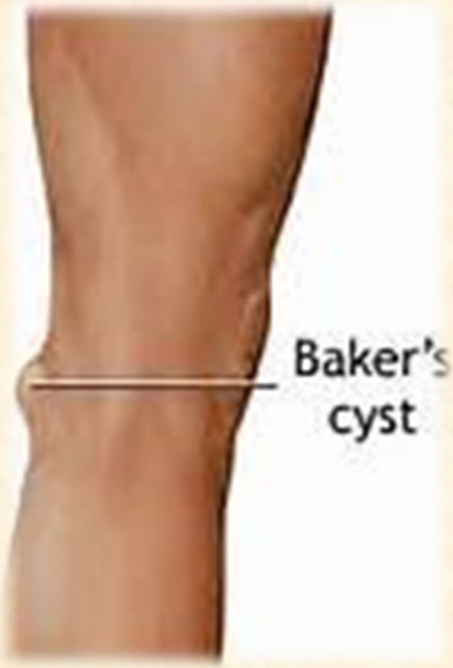
Chronic venous insufficiency is a cause of long-standing oedema that, particularly when combined with another cause of leg swelling, may acutely worsen. Characteristic skin changes (haemosiderin deposition, hair loss, varicose eczema, ulceration) and prominent varicosities are common, and sometimes cause diagnostic confusion with cellulitis.


Deep Veins of the Leg
Normal Blood Flow
Deep Vein Thrombosis
Embolus

Differential Diagnosisof unilateral leg swelling

1. Spontaneous or traumatic calf muscle tear.
2. Ruptured Baker's cyst, both characterised by
   a) Sudden onset
   b) Localised tenderness. Baker's cysts usually occur in patients with rheumatoid arthritis.
3. Infective cellulitis is usually distinguished by:

   a) Marked skin erythema
   b) Heat which is localised within a well-demarcated area of the leg
   c) May be associated with an obvious source of entry of infection (e.g. an insect bite or leg ulcer).



Clinical criteria can be used to rank patients according to their likelihood of DVT using the Wells scoring system

Predicting the pre-test probability of deep vein thrombosis (DVT) using the Wells score*

Clinical characteristic Score

1-Previous documented DVT 1

2-Active cancer (patient receiving treatment for cancer within previous 6 months or currently receiving palliative treatment) 1

3-Paralysis, paresis or recent plaster immobilisation of lower extremities 1

4-Recently bedridden for ≥ 3 days, or major surgery within previous 12 weeks 1

5-Localised tenderness along distribution of deep venous system 1

6-Entire leg swollen 1

7-Calf swelling at least 3 cm larger than that on asymptomatic side (measured 10 cm below tibial tuberosity) 1

8-Pitting oedema con□ned to symptomatic leg 1

9-Collateral superficial veins (non-varicose) 1

10-Alternative diagnosis at least as likely as DVT –2

Clinical probability Totalscore

DVT low probability < 1

DVT moderate probability 1–2

DVT high probability > 2

*A dichotomised revised Wells score, which classifies patients as 'unlikely' or 'likely', may be used.

From Wells PS. Evaluation of D-dimer in the diagnosis of suspected deep vein thrombosis. N

Engl J Med 2003; 349:1227;

In patients with a low (‘unlikely’) pre-test probability of DVT, D-dimer levels can be measured; if these are normal, further investigation for DVT is unnecessary.
In those with a moderate or high (‘likely’) probability of DVT or with elevated D-dimer levels, objective diagnosis of DVT should be obtained using appropriate imaging, usually a Doppler ultrasound scan.

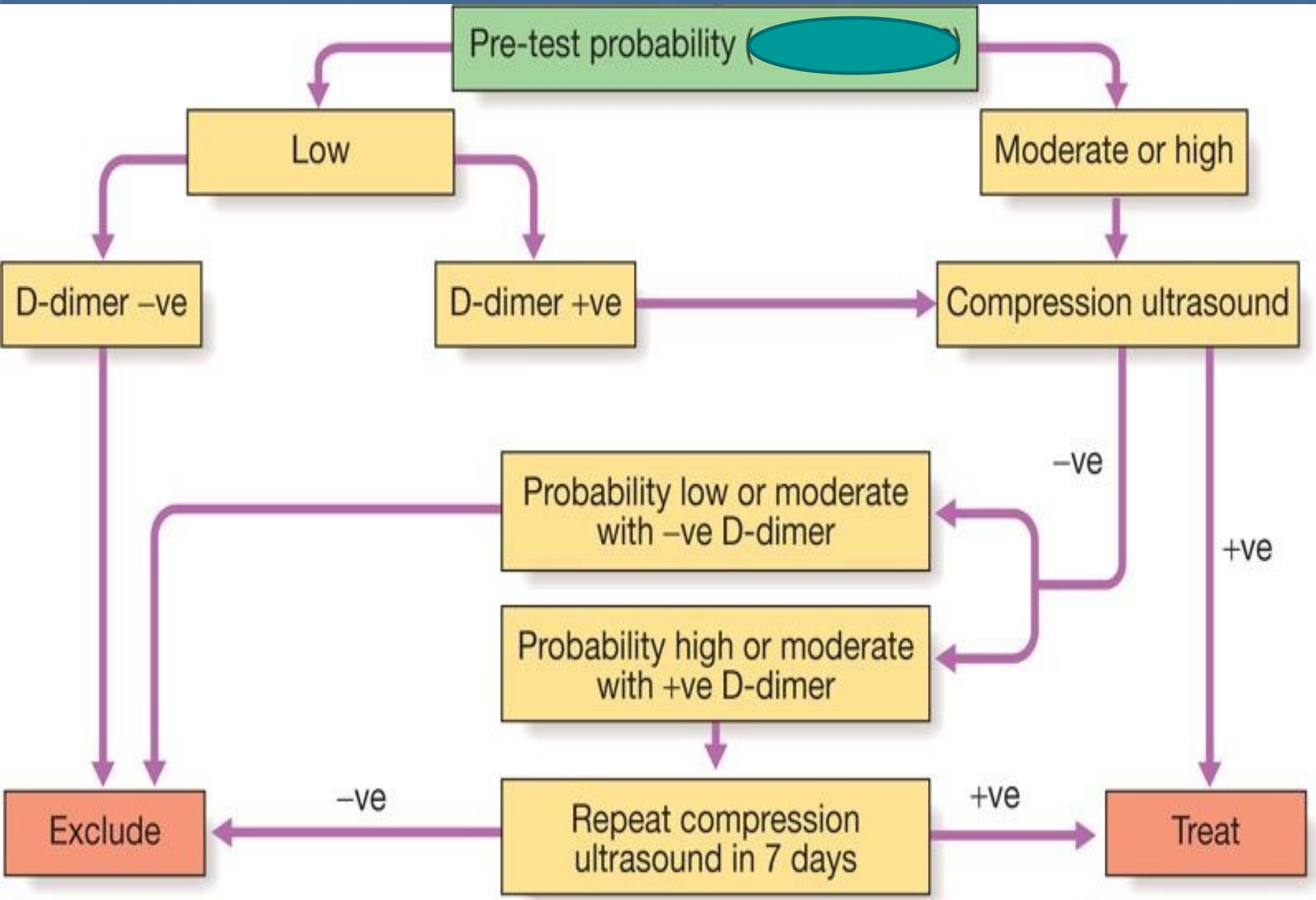
the investigative pathway for DVT according to the pre-test probability of DVT.

1-For low-probability DVT, the negative predictive value
of the D-dimer test (the most important parameter in this context) is over 99%; if the test is negative, the clinician can discharge the patient with confidence.

2-In patients with a high probability of DVT, the negative predictive value of a D-dimer test falls to somewhere in the region of 97%–98%. While this may initially appear to be a high figure, to discharge 2 or 3 patients in every 100 incorrectly would generally be considered an unacceptable error rate. Hence, with the exception of pregnancy , a combination of clinical probability and blood test results should be used in the diagnosis of DVT.

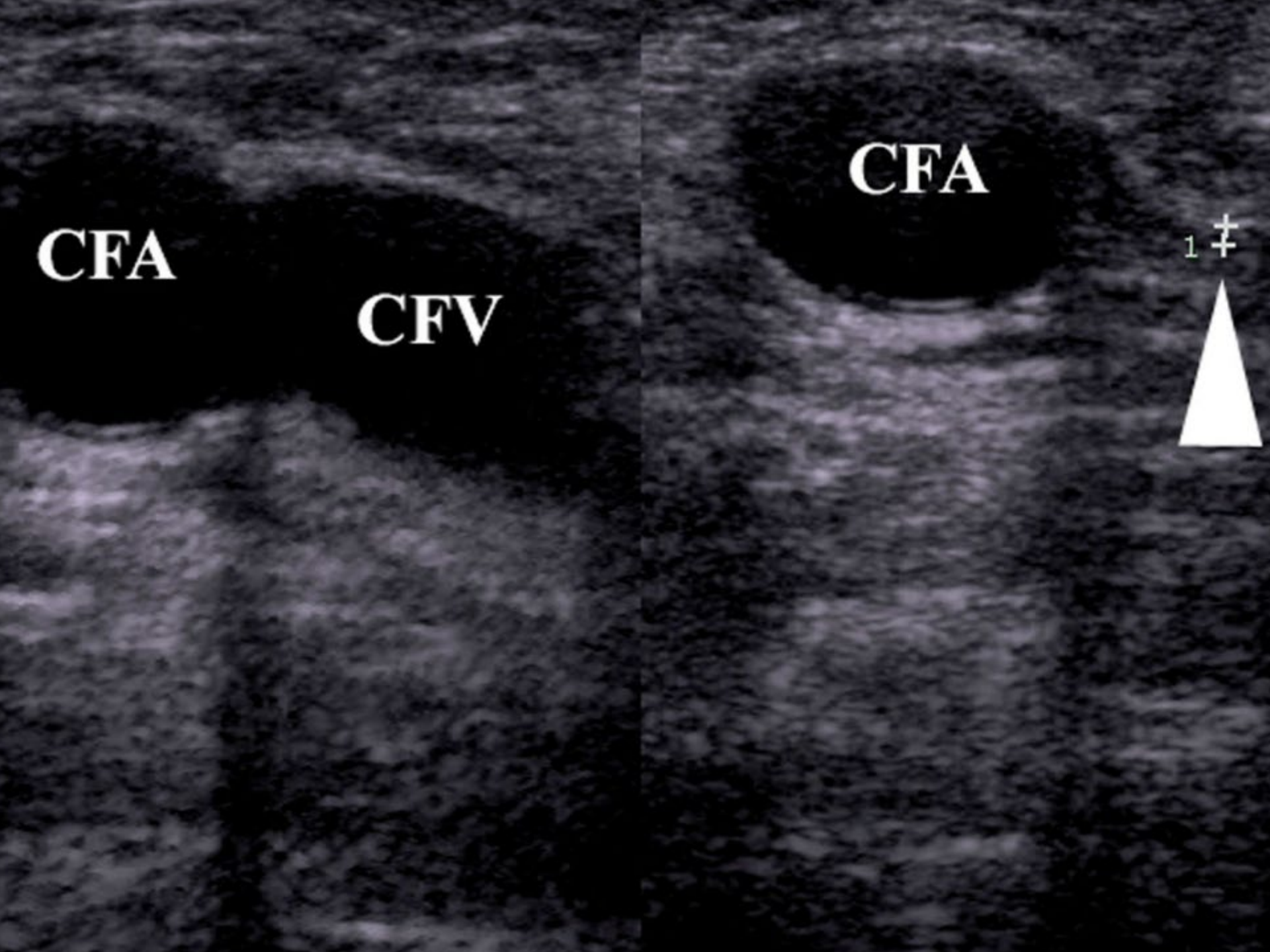
If cellulitis is suspected, serum inflammatory markers, skin swabs and blood cultures should be sent, ideally before antibiotics are given.
Ruptured Baker's cyst and calf muscle tear can both be readily diagnosed on ultrasound.

If pelvic or lower abdominal malignancy is suspected, a prostate-specific antigen (PSA) level should be measured in males and appropriate imaging with ultrasound (transabdominal or transvaginal) or CT should be undertaken.



Compression ultrasound is the imaging modality of choice in most centres.
It has a sensitivity for proximal DVT (clot involving the popliteal vein or above) of 99.5%.
Sensitivity & specificity are lower for diagnosing calf vein thrombosis.
Contrast venography is an alternative that is now rarely used.

In patients with proven DVT, further imaging to diagnose PE is not required unless massive PE is clinically suspected or there is otherwise unexplained breathlessness .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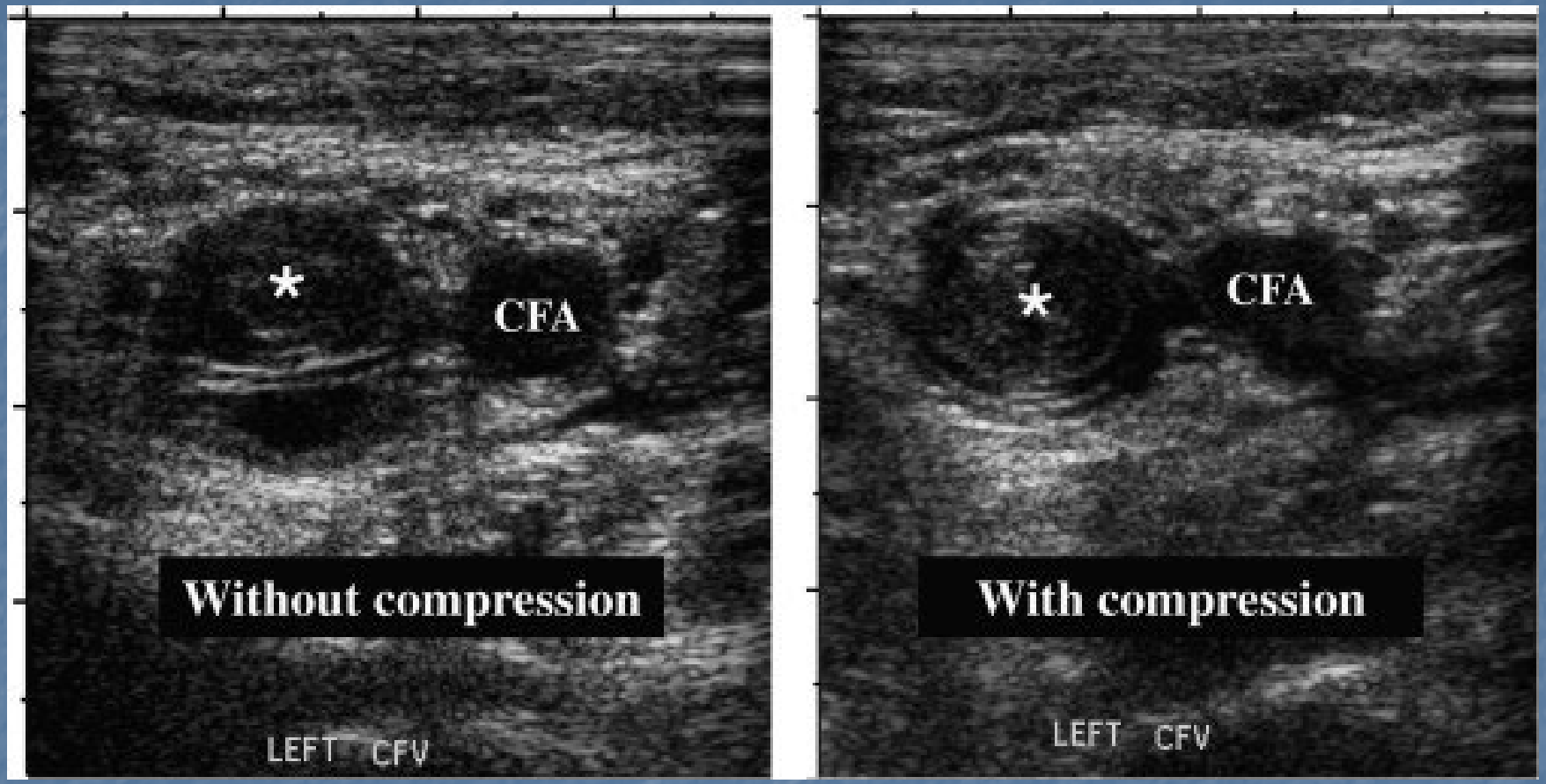
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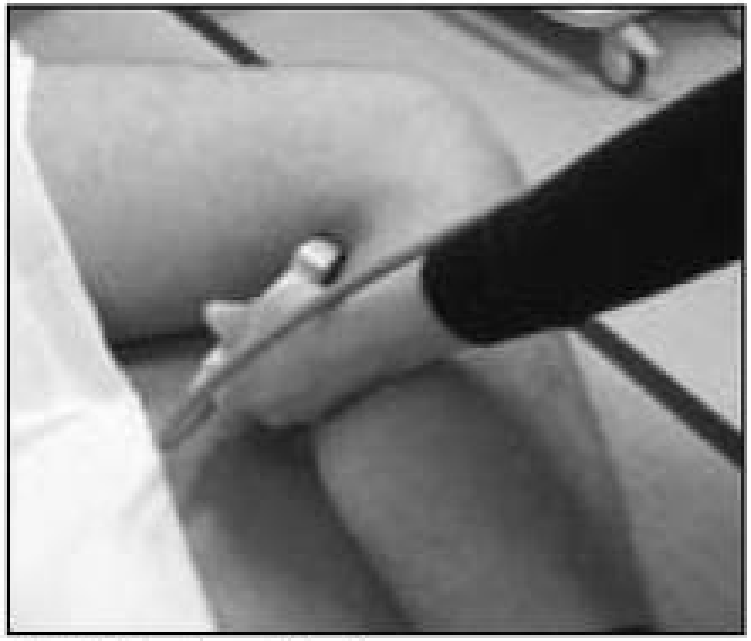
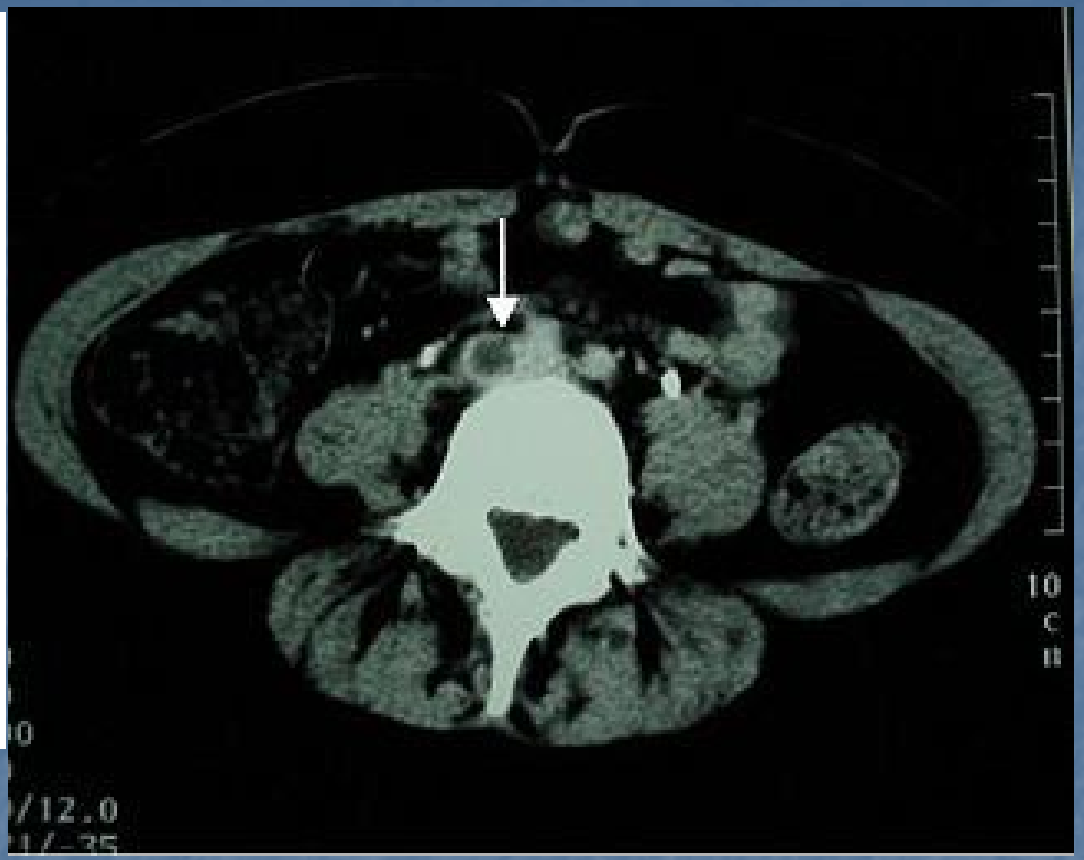
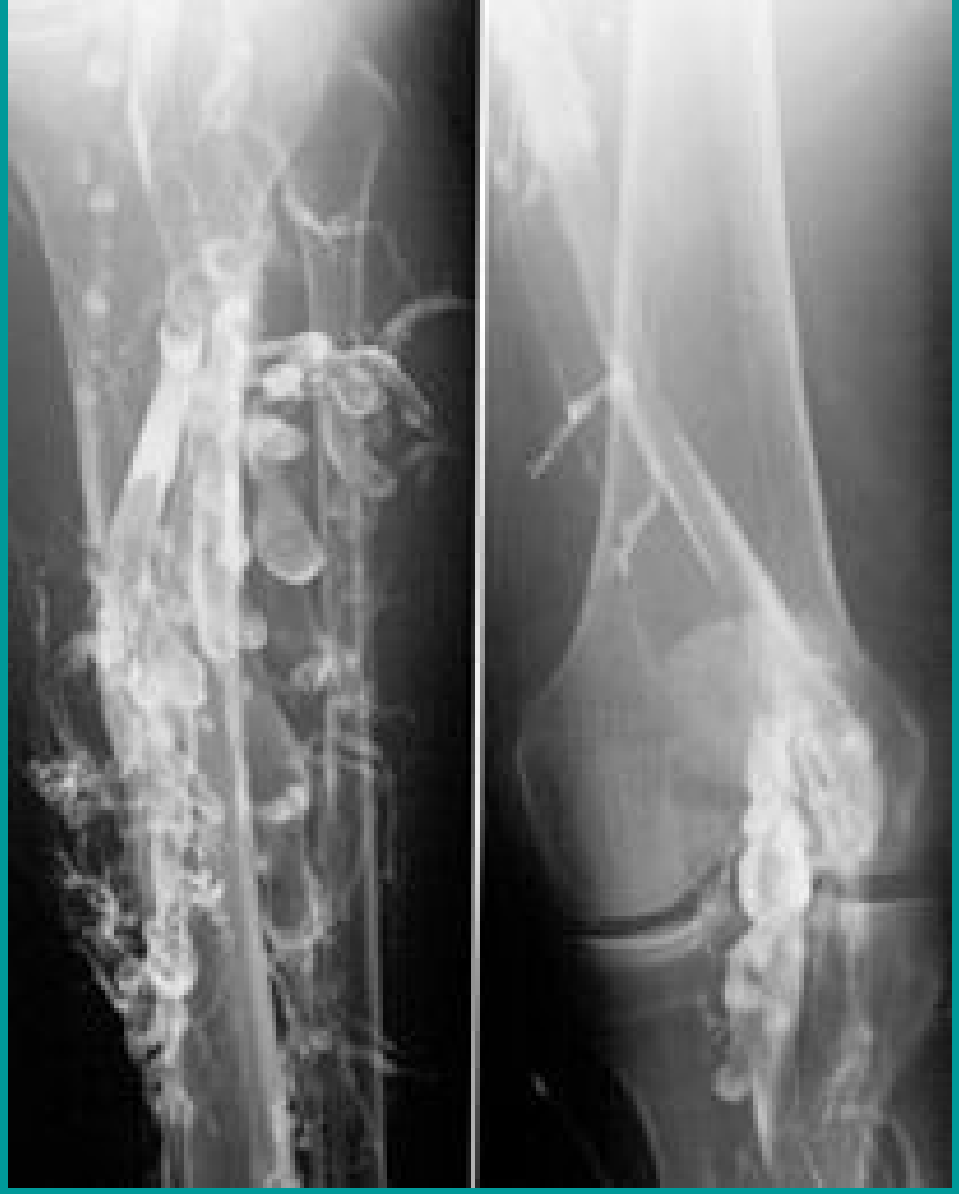


2) Patient positioning.



An abdominal CT scan with a clot in the right common iliac vein



Venograms of DVT

Management of VTE

The mainstay of treatment for all forms of VTE is anticoagulation. This can be achieved in several ways.

1- One option is to use LMWH followed by a coumarin anticoagulant, such as warfarin. Treatment of acute VTE with LMWH should continue for a minimum of 5 days. Patients treated with warfarin should achieve a target INR of 2.5 (range 2–3) with LMWH continuing until the INR is above 2.

2-Alternatively, patients may be treated with a DOAC. Rivaroxaban and apixaban may be used immediately from diagnosis without the need for LMWH, while the licences for dabigatran and edoxaban include initial treatment with LMWH for a minimum of 5 days before commencing the DOAC.

3-In patientswith active cancer and VTE, there is evidence that maintenance anticoagulation with LMWH is associated with a lower recurrence rate than warfarin.

4-Patients who have had VTE and have a strong contraindication to anticoagulation and those who continue to have new pulmonary emboli despite therapeutic anticoagulation should have an inferior vena cava (IVC) filter inserted to prevent life-threatening PE .

The optimal initial period of anticoagulation is between 6 weeks and 6 months .

5-Patients with provoked VTE in the presence of a temporary risk factor, which is then removed, can usually be treated for short periods (e.g. 3 months), and indeed anticoagulation for more than 6 months does not alter the rate of recurrence following discontinuation of therapy.

If there are ongoing risk factors that cannot be alleviated, such as active cancer, long-term anticoagulation is usually recommended, provided that the risk of bleeding is not deemed excessive.

For patients with unprovoked VTE, the optimum duration of anticoagulation can be difficult to establish. Recurrence of VTE is about 2–3% per annum in patients who have a temporary medical risk factor at presentation and about 7–10% per annum in those with apparently unprovoked VTE.
This plateaus at around 30–40% recurrence at 5 years. As such, many patients who have had unprovoked episodes of VTE will benefit from long-term anticoagulation.

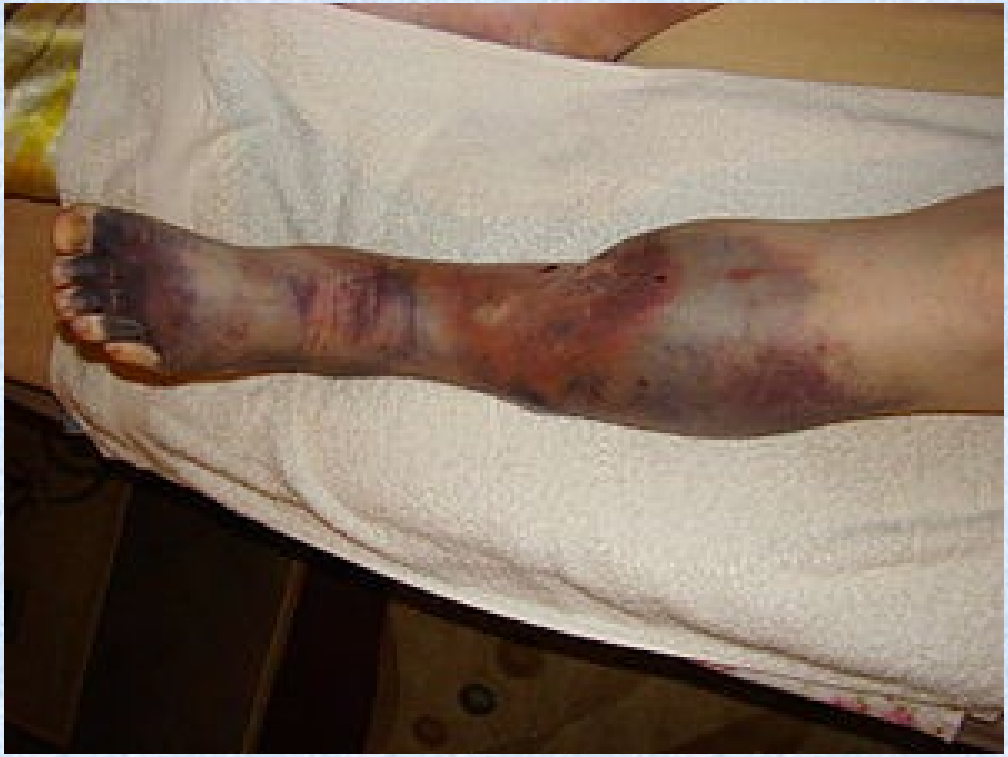
Several factors predict risk of recurrence following an episode of unprovoked VTE.
The strongest predictors of recurrence are:
-male sex and
- a positive D-dimer assay measured
1 month after stopping anticoagulant therapy.
These factors are incorporated into scoring systems to predict recurrence such as the DASH score and the Vienna prediction model.

The management of DVT of the leg should also include elevation and analgesia; in limb-threatening DVT, thrombolysis may also be considered.

Post-thrombotic syndrome is due to damage of venous valves by the thrombus. It occurs in around 30% of patients who sustain a proximal lower limb DVT and results in persistent leg swelling, heaviness and discoloration.

The most severe complication of this syndrome is ulceration around the medial malleolus .

Recent trial evidence suggests that use of elastic compression stockings following a DVT does not reduce the incidence of post-thrombotic syndrome



Prophylaxis of VTE

All patients admitted to hospital should be assessed for their risk of developing VTE and appropriate prophylactic measures should be put in place.

Both medical and surgical patients are at increased risk.

Early mobilisation of patients is important to prevent DVT, and those at medium or high risk require additional antithrombotic measures; these may be pharmacological or mechanical.

There is increasing evidence in high-risk groups: patients who have had major lower limb orthopaedic surgery and abdominal or pelvic cancer surgery, for protracted thromboprophylaxis for as long as 30 days or so after the procedure.

Particular care should be taken with the use of pharmacological prophylaxis in patients with a high risk of bleeding or with specific risks of haemorrhage related to the site of surgery or the use of spinal or epidural anaesthesia

Antithrombotic prophylaxis

Indications

Patients in the following categories should be considered for specific antithrombotic prophylaxis:

Moderate risk of DVT

Major surgery

- In patients > 40 yrs or with other risk factor for VTE

Major medical illness, e.g.

- Heart failure
- MI with complications
- Sepsis
- Inflammatory conditions, including inflammatory bowel disease
- Active malignancy
- Nephrotic syndrome
- Stroke and other conditions leading to lower limb paralysis

High risk of DVT

- Major abdominal or pelvic surgery for malignancy or with history of DVT or known thrombophilia (see Box 24.4, p. 1001)
- Major hip or knee surgery
- Neurosurgery

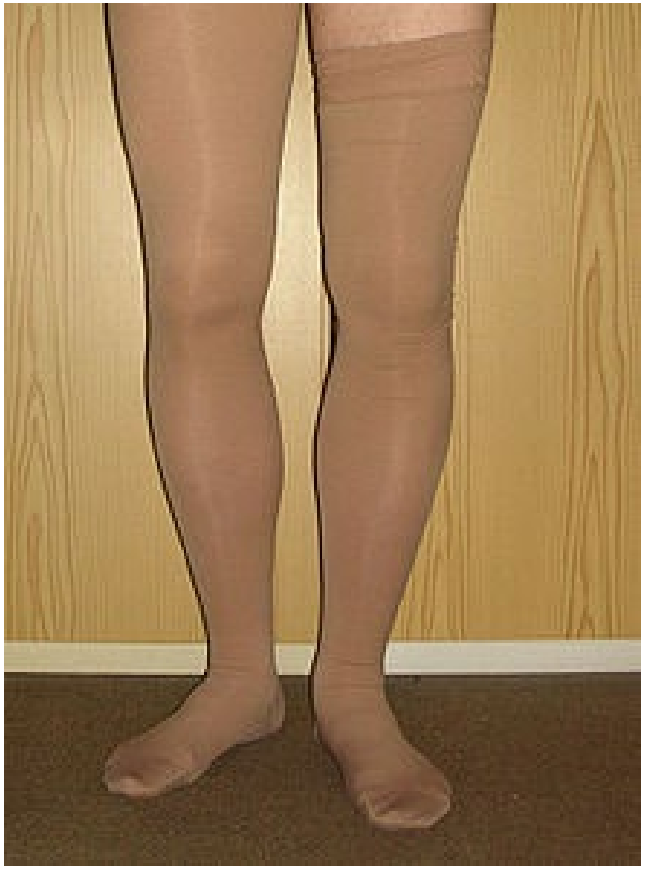
Methods of VTE prophylaxis

Mechanical

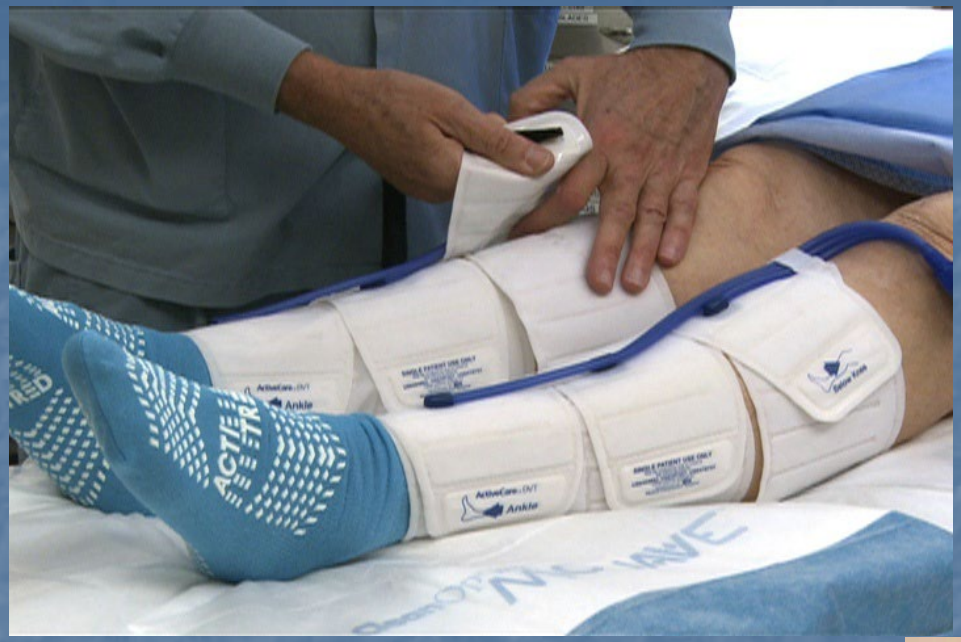
Intermittent pneumatic compression
Mechanical foot pumps

Graduated compression stockings

The ACCP suggested graduated compression stockings for at-risk travelers and some hospital patients.



IPC pumps and garments provide a safe and effective method of preventing Venous Thromboembolism (VTE) by replicating what the body does naturally.


ActiveCare DVT
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ActiveCare DVT
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Pharmacological

-Low molecular weight heparins
-Unfractionated heparin
-Fondaparinux
-Dabigatran
-Revaroxaban
–Apixaban
-Warfarin

Inherited and acquired thrombophilia and prothrombotic states

Several inherited conditions predispose to VTE and have several points in common that are worth noting:

- None of them is strongly associated with arterial thrombosis.
- All are associated with a slightly increased incidence of adverse outcome of pregnancy, including recurrent early fetal loss, but there are no data to indicate that any specific intervention changes that outcome.

•Apart from in antithrombin deficiency and homozygous factor V Leiden, most carriers of these genes will never have an episode of VTE; if they do, it will be associated with the presence of an additional temporary risk factor.

• There is little evidence that detection of these abnormalities predicts recurrence of VTE.

• None of these conditions per se requires treatment with anticoagulants.

Antithrombin deficiency

Antithrombin (AT) is a serine protease inhibitor (SERPIN) that inactivates the activated coagulation factors IIa, IXa, Xa and XIa. Heparins and fondaparinux achieve their therapeutic effect by potentiating the activity of AT.

Familial deficiency of AT is inherited in an autosomal dominant manner; homozygosity for mutant alleles is not compatible with life.

Around 70% of affected individuals will have episode of VTE before the age of 60 years and the relative risk for thrombosis compared with the background population is 10–20 fold.

Pregnancy is a high-risk period for VTE and this requires fairly aggressive management with doses of LMWH that are greater than the usual prophylactic doses (≥ 100 U/kg/day). AT concentrate (either plasma-derived or recombinant) is available; this is required for cardiopulmonary bypass and may be used as an adjunct to heparin in surgical prophylaxis and in the peripartum period.

Protein C and S deficiencies

Protein C and its co-factor protein S are vitamin K-dependent natural anticoagulants involved in switching off coagulation factor activation (factors Va and VIIIa) and thrombin generation .

Inherited deficiency of either protein C or S results in a prothrombotic state with a fivefold relative risk of VTE compared with the background population.

Antiphospholipid syndrome

Antiphospholipid syndrome (APS) is a clinicopathological entity in which a constellation of clinical conditions, alone or in combination, is found in association with a persistently positive test for an antiphospholipid antibody.

The antiphospholipid antibodies are heterogeneous and typically are directed against proteins that bind to phospholipids.

In clinical practice, two types of test are used, which detect:

- Antibobies that bind to negatively charged phospholipid on an ELISA plate (called an anticardiolipin antibody test). These assays usually contain β2-glycoprotein 1 (β2-GP1)
- Those that interfere with phospholipid-dependent coagulation tests like the APTT or the dilute Russell viper venom time (DRVVT; called a lupus anticoagulant test).

The term antiphospholipid antibody encompasses both a lupus anticoagulant and an anticardiolipin antibody/ anti-β2-GP1; individuals may be positive for one, two or all three of these activities. It has been shown that patients who are 'triple-positive' have an increased likelihood of thrombotic events.

Clinical features and management

APS may present in isolation (primary APS) or in association with one of the conditions shown below, most typically SLE (secondary APS).

Most patients present with a single manifestation and APS is now most frequently diagnosed in women with adverse outcomes of pregnancy.

Conditions associated with secondary APS

- **Systemic lupus erythematosus**
- **Rheumatoid arthritis**
- **Systemic sclerosis**
- **Behçet's disease**
- **Temporal arteritis**
- **Sjögren's syndrome**

Clinical manifestations

- Adverse pregnancy outcome:

Recurrent first trimester abortion (≥ 3), unexplained death of morphologically normal fetus after 10 weeks' gestation, severe early pre-eclampsia

- Venous thromboembolism
- Arterial thromboembolism
- Livedo reticularis, catastrophic APS, transverse myelitis, skin necrosis, chorea.

Targets for antiphospholipid antibodies

***β_2-glycoprotein 1**
***Protein C**
***Annexin V**
***Prothrombin (may result in haemorrhagic presentation)**

It is extremely important to make Diagnosis in patients with APS, whatever the manifestation, because it affects the prognosis and management of arterial thrombosis, VTE and pregnancy.
Arterial thrombosis, typically stroke, associated with APS should probably be treated with **warfarin** as opposed to **aspirin**.
APS-associated VTE is one of the situations in which the predicted recurrence rate is high enough to indicate long-term anticoagulation after a first event.

Recent evidence suggests that patients with APS presenting with thrombotic events should receive warfarin as opposed to a DOAC as anticoagulant of choice. In women with obstetric presentations of APS, intervention with heparin and aspirin is almost routinely prescribed, although there is little evidence from clinical trials that it is an effective therapy in increasing the chance of a successful pregnancy outcome.

Thank you