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Pulmonary embolism

What is a pulmonary embolism?

A pulmonary embolism (PE) is a blood clot that obstructs the pulmonary artery or its branches.

> **Pulmonary embolism (PE) is a medical emergency**. It may present with very few clinical signs and/or symptoms, making it easy to miss, and a high index of suspicion is warranted.

PEs are usually embolic, ie caused by a mass that has originated elsewhere and travelled through blood vessels to reach the pulmonary artery tree.

The emboli can be caused by:

- Thrombosis - accounts for the majority of cases and has usually arisen from a distant vein and travelled to the lungs via the venous system.
- Fat - following long bone fracture or orthopaedic surgery.
- Amniotic fluid.[1]
- Air - following neck vein cannulation or bronchial trauma.

Pulmonary thrombi may also develop de novo in the pulmonary arteries, termed in-situ pulmonary thrombosis.[2]

The rest of this article deals with thrombotic PE.

How common is pulmonary embolism? (Epidemiology)

The incidence of pulmonary embolism in the UK varies from 7-8 per 10,000 people, per year.[3]

Risk factors[4]

Clots form when one or more of the following factors are present: increased blood coagulability, reduced mobility or blood vessel abnormalities. These correspond to some of the risk factors for VTE (see below). A number of patients may not have any risk factors, making the diagnosis difficult.

Strong risk factors (OR > 10)

- Lower limb fractures.
- Recent hospitalisation for heart failure or atrial fibrillation or flutter (within past 3 months).
- Major trauma.
- Hip or knee replacement.
- Myocardial infarction within the previous 3 months.
- Spinal cord injury.
- Previous VTE.

Moderate risk factors (OR 2-9)

- Arthroscopic knee surgery.
- Autoimmune diseases.
- Blood transfusion.
- Central venous lines.
- Intravenous catheters and leads.

- Chemotherapy.
- Congestive heart failure or respiratory failure
- Erythropoiesis-stimulating agents.
- Oral hormone replacement therapy.[5]
- *In vitro* fertilization.
- Combined hormonal contraception.
- Post-partum state.
- Infection (specifically pneumonia, urinary tract infection, and HIV).
- Inflammatory bowel disease.
- Cancer (highest risk in metastatic disease).
- Paralytic stroke.
- Superficial vein thrombosis.
- Thrombophilias.

Weak risk factors (OR 2-9)

- Bed rest >3 days.
- Diabetes mellitus.
- Hypertension.
- Immobility due to sitting (eg, prolonged car or air travel).
- Increasing age.
- Laparoscopic surgery (eg, cholecystectomy).
- Obesity.
- Pregnancy
- Varicose veins.

Symptoms of pulmonary embolism (presentation)[6]

The symptoms and signs of PE are not specific. Severe cases of PE can lead to collapse or sudden death. Some PEs are rapidly fatal. In a large proportion of fatal cases, the PE is not clinically diagnosed prior to death.[7]

Symptoms include:

- Dyspnoea.
- Pleuritic chest pain, retrosternal chest pain.
- Cough and haemoptysis.
- Any chest symptoms in a patient with symptoms suggesting a deep vein thrombosis (DVT).
- In severe cases, right heart failure causes dizziness or syncope.

Signs include:

- Tachypnoea, tachycardia.
- Hypoxia, which may cause anxiety, restlessness, agitation and impaired consciousness.
- Pyrexia.
- Elevated jugular venous pressure.
- Gallop heart rhythm, a widely split second heart sound, tricuspid regurgitant murmur.
- Pleural rub.
- Systemic hypotension and cardiogenic shock.

PEs may also be asymptomatic.

Differential diagnosis

Other causes of collapse, chest pain or dyspnoea - importantly:

- Acute coronary syndromes.
- Aortic dissection - especially as anticoagulation might be fatal.
- Cardiac tamponade.
- Pneumonia.
- Pneumothorax.
- Sepsis.

Assessment[6]

NB: treatment may precede investigations if the patient is very ill (see 'Initial management' below).

National Institute for Health and Care Excellence (NICE) recommendations

- If a patient presents with signs or symptoms of PE, carry out an assessment of their general medical history, a physical examination and CXR to exclude other causes.
- If clinical suspicion for PE is low, use the pulmonary embolus rule-out criteria to determine if further investigation of PE is indicated.[8]
- If PE is suspected, use the two-level PE Wells' score to estimate the clinical probability of PE (see below).
- Offer patients in whom PE is suspected and with a likely two-level PE Wells' score (more than 4 points) an immediate computerised tomography pulmonary angiogram (CTPA).
- If a CTPA cannot be carried out immediately or is contra-indicated, offer immediate interim parenteral anticoagulant therapy followed by a CTPA.

- Consider a proximal leg vein ultrasound scan if the CTPA is negative and DVT is suspected. If the scan is negative consider alternative diagnoses but ensure the person is aware of the signs and symptoms of PE and that they should seek immediate medical help if these develop.
- Offer patients in whom PE is suspected and with a two-level PE Wells' score less than 4 points a D-dimer test with the result available within four hours if possible. If the result is not available within four hours, offer interim therapeutic anticoagulation.
- If the result is positive, offer either an immediate CTPA or immediate interim parenteral anticoagulant therapy followed by a CTPA, if a CTPA cannot be carried out immediately.
- If the result is negative, stop immediate interim anticoagulation, consider alternative diagnoses and warn patients to look out for the signs and symptoms of PE.
- For patients who have an allergy to contrast media, or who have severe renal impairment (estimated creatinine clearance less than 30 ml/min), or whose risk from irradiation is high:
    - Assess the suitability of a ventilation/perfusion single-photon emission computerised tomography (V/Q SPECT) scan or, if a V/Q SPECT scan is not available, a V/Q planar scan, as an alternative to CTPA.
    - If offering a V/Q SPECT or planar scan that will not be available immediately, offer immediate interim parenteral anticoagulant therapy.
- Diagnose PE and treat patients with a positive CTPA or in whom PE is identified with a V/Q SPECT or planar scan. Offer or continue anticoagulation treatment, or if anticoagulation treatment is contra-indicated, consider a mechanical intervention.

- Consider alternative diagnoses in the following two groups of patients:
    - Patients with an unlikely two-level PE Wells' score and either a negative D-dimer test, or a positive D-dimer test and a negative CTPA.
    - Patients with a likely two-level PE Wells' score and both a negative CTPA and no suspected DVT.
- Offer all patients diagnosed with unprovoked PE (defined as PE in a person with no recent major clinical risk factor for PE, who is not taking the combined oral contraceptive pill or hormone replacement therapy), who are not already known to have cancer the following investigations for cancer:
    - Physical examination guided by a full and thorough history.
    - CXR.
    - Blood tests (FBC, renal function, serum calcium, PT and APTT, and LFTs).
    - Urinalysis.
- Consider further investigations for cancer with an abdomino-pelvic CT scan (and a mammogram for women) in all patients aged over 40 years with a first unprovoked PE who do not have signs or symptoms of cancer based on initial investigation.
- Consider testing for antiphospholipid antibodies in patients who have had unprovoked PE if it is planned to stop anticoagulation treatment. Be aware that these tests can be affected by anticoagulants and be prepared to seek specialist advice if indicated.
- Consider testing for hereditary thrombophilia in patients who have had unprovoked PE and who have a first-degree relative who has had DVT or PE, if it is planned to stop anticoagulation treatment.

Risk score

Assessment of the clinical probability of VTE is recommended, as it is relevant when interpreting clinical findings and deciding how to investigate. NICE recommends the Wells' score but other scoring systems have also been developed.

Wells' Two-level PE Score

Clinical feature	Point
Clinically suspected DVT (minimum leg swelling and pain on palpation of deep veins).	3.0
Alternative diagnosis less likely than PE.	3.0
Tachycardia (heart rate above 100 beats per minute).	1.5
Immobilisation for more than three days or surgery in the previous four weeks.	1.5
History of DVT or PE.	1.5
Haemoptysis.	1.0
Malignancy (on treatment in the preceding six months or palliative stage).	1.0

Clinical probability

- 4 points or fewer = PE unlikely.
- More than 4 points = PE likely.

For patients with a score of 4 points or fewer, use the PERC rule. Where there is a low clinical probability of PE, meeting all criteria of the PERC rule allows PE to be effectively ruled-out without further investigation. [4]

Diagnosing pulmonary embolism (investigations)

General investigations [4]

- **Baseline investigations** - as for any ill patient: oxygen saturation, FBC, biochemistry, baseline clotting screen. Troponin and brain natriuretic peptide levels may also be elevated.

- **ECG** - may be normal, or show any of these changes: sinus tachycardia, atrial fibrillation, nonspecific ST or T-wave abnormalities, right ventricular strain pattern V1-3, right axis deviation, right bundle branch block (RBBB), or deep S-waves in I with Q waves in III and inverted T waves in III ('S1,Q3,T3' pattern). A large PE can show ECG features of acute cardiac ischaemia (eg, ST depression).[9]

- **CXR** - mainly useful to exclude other chest disease, and is needed for interpreting V/Q scans. It is usually normal, but may show: decreased vascular markings, atelectasis or a small pleural effusion. An occasional late sign may be an homogeneous wedge-shaped area of pulmonary infarction in the lung periphery (Hampton's hump) with its base contiguous to a visceral pleural surface and its rounded convex apex directed toward the hilum.

- **Arterial blood gases** - may show reduced PaO_2, reduced $PaCO_2$ due to hyperventilation or acidosis.

- **Echocardiography** - may show thrombus in proximal pulmonary arteries and, if normal, can exclude haemodynamically important PE. It cannot exclude smaller PEs. It may show signs of right ventricular strain or right ventricular hypokinesis.

- **Cardiac troponins** - can be indicative of right heart strain.

- **D-dimers** - fibrin D-dimer is a degradation product of cross-linked fibrin. The concentration increases in patients with acute VTE and provides a very sensitive test to exclude acute DVT or PE. D-dimer tests have less specificity and are less useful in some groups of patients - eg, those with high clinical probability; those admitted to hospital for another reason, in whom the suspicion of PE is raised during their hospital stay; individuals older than 65 years; pregnant women.[10]

    - Age-adjusted D-dimer cutoffs may improve the specificity of the test in older people, without sacrificing sensitivity.[4]

Specific investigations for VTE [4] [6]

The choice and order of investigations will depend on the clinical likelihood of PE, how ill the patient is and availability of the test. The 'gold standard' test is CTPA. An explanation of the scope of each test helps in understanding these strategies:

- **Leg ultrasound**: in patients with co-existing clinical DVT, lower-limb ultrasound as the initial imaging test is often sufficient to confirm VTE - and hence to start anticoagulation. However, a single normal leg ultrasound cannot exclude DVT.
- **CTPA** has become the method of choice for imaging the pulmonary vasculature in patients with suspected PE.
- **Isotope lung scanning (V/Q scan)**: although there have been controversies about the accuracy of isotope scans, they are reliable enough to exclude or confirm PE, if performed according to UK protocols. However, if the result is 'indeterminate', further imaging is needed. For this reason, V/Q scanning is reserved for patients in whom CTPA is contra-indicated.

Management of pulmonary embolism

Initial resuscitation and supportive therapy

- Oxygen 100%.
- Obtain IV access, monitor closely, start baseline investigations.
- Give analgesia if necessary (eg, morphine).
- Assess circulation: suspect massive PE if systolic BP is <90 mm Hg or there is a fall of 40 mm Hg, for 15 minutes, not due to other causes.
    - Consider cautious volume replacement if hypovolaemic, or vasopressor or inotropic support.[5]

- In cardiac arrest suspected to be caused by an acute PE, follow standard advanced life support guidelines, and consider giving thrombolytic therapy. Cardiopulmonary resuscitation should continue for at least 60-90 minutes after a thrombolytic drug has been administered, before terminating resuscitation attempts.[4]
- Extracorporeal membrane oxygenation (ECMO) may be helpful for temporary support of patients with high-risk PE and circulatory collapse or cardiac arrest, as a bridge to further treatment (eg, surgical embolectomy).[4]

Anticoagulation therapy[6]

- Outpatient anticoagulation may be considered for patients with low-risk PE, providing they are supplied with all the necessary information.
- Offer anticoagulation to patients with confirmed PE for at least three months.
- If not already available, arrange baseline investigations (see above).
- Offer apixaban or rivaroxaban to patients with confirmed PE.[3]
    - If neither of these is suitable offer a choice of low molecular weight heparin (LMWH) for five days followed by dabigatran or edoxaban; **or**
    - LMWH concurrently with a vitamin K antagonist (VKA) for at least five days, or until the INR is at least 2.0 in two consecutive readings, followed by a VKA on its own.

- Offer people with confirmed PE and renal impairment (estimated creatinine clearance between 15 ml/min and 50 ml/min) one of:
    - Apixaban.
    - Rivaroxaban.
    - LMWH for at least five days followed by edoxaban or dabigatran if estimated creatinine clearance is 30 ml/min or above.
    - LMWH or UFH, given concurrently with a VKA for at least five days or until the INR is at least 2.0 in two consecutive readings, followed by a VKA on its own.
- Offer people with confirmed PE and renal failure (estimated creatinine clearance less than 15 ml/min) one of:
    - LMWH.
    - UFH.
    - LMWH or UFH concurrently with a VKA for at least five days or until the INR is at least 2.0 in two consecutive readings, followed by a VKA on its own.
- Consider anticoagulation for people with PE who have extreme body weight (less than 50 kg or more than 120 kg) but ensure regular monitoring and dosage adjustment as per manufacturer's instructions and local protocols. Offer people with confirmed PE and an established diagnosis of triple positive antiphospholipid syndrome LMWH concurrently with a VKA for at least five days, or until the INR is at least 2.0 in two consecutive readings, followed by a VKA on its own.
- People with confirmed PE and an established diagnosis of triple positive antiphospholipid syndrome should be offered LMWH concurrently with a VKA for at least five days, or until the INR is at least 2.0 in two consecutive readings, followed by a VKA on its own.

- Offer a direct-acting oral anticoagulant (DOAC) to patients with active cancer (receiving active antimitotic treatment; or diagnosed within the previous six months; or recurrent or metastatic; or inoperable) and confirmed PE, and continue for six months. At six months, assess the risks and benefits of continuing anticoagulation. Take into account the tumour site, interactions with other drugs, including those used to treat cancer, and the person's bleeding. If a DOAC is unsuitable, consider LMWH alone or LMWH concurrently with a VKA[5] for at least five days, or until the INR is at least 2.0 in two consecutive readings, followed by a VKA on its own.
- Offer a vitamin K antagonist (VKA) to patients with confirmed PE within 24 hours of diagnosis and continue the VKA for three months. At three months, assess the risks and benefits of continuing VKA treatment.
- Offer a VKA beyond three months to patients with an unprovoked PE, taking into account the patient's risk of VTE recurrence and whether they are at increased risk of bleeding.

Provide patients who are having anticoagulation treatment with an anticoagulant information booklet and an anticoagulant alert card and advise them to carry the anticoagulant alert card at all times.

Anticoagulant treatment should be reviewed at 3 months after VTE, and at least once a year thereafter if used long-term.[11]

Other treatments[6]

- For people with confirmed PE and haemodynamic instability, offer continuous UFH infusion and consider thrombolytic therapy.
    - Thrombolytic therapy can be given systemically, or directly into the pulmonary artery using percutaneous catheter-directed treatment. Catheter-directed treatment often combines mechanical thrombectomy or fragmentation with in situ thrombolysis.[4]
    - The evidence base is currently stronger for systemic thrombolysis.[4]
- Inferior vena caval filters should be offered to patients with PE:
    - Only as part of a clinical study or when anticoagulation is contra-indicated.
    - When arrangements can be made to remove the filter as soon as clinically appropriate.
- Surgical embolectomy has been performed for high-risk PE, and also for selected patients with intermediate- or high-risk PE, particularly if thrombolysis is contra-indicated or has failed. Surgical embolectomy has also been successfully performed in patients with right heart thrombi straddling the interatrial septum through a patent foramen ovale.[4]

Pregnancy[4]

PE is the one of the leading causes of maternal death in developed countries. The risk of PE is higher in the postpartum period, particularly after a caesarean section. Pregnancy does not alter the clinical features of PE but, as pregnant women often experience some degree of breathlessness,[12] this symptom should be interpreted with caution.

See the separate Venous thromboembolism in pregnancy article.

Complications and prognosis

- If left untreated, the prognosis for PE is poor. Even when treated, some patients develop chronic thromboembolic pulmonary hypertension, which is caused by obstruction of the pulmonary arteries due to PE. This puts excessive pressure on the heart, which can cause heart failure.[6]
- In the International Cooperative Pulmonary Embolism Registry, the all-cause mortality rate at three months associated with acute PE was 17%. PE was considered to be the cause of death in 45% of patients.[10]
- Important prognostic factors associated with death from PE were age older than 70 years, cancer, congestive heart failure, COPD, systolic arterial hypotension, tachypnoea, and right ventricular hypokinesis on echocardiography.[10]
- The mortality rate is lower in those who are haemodynamically stable and higher in those who present in cardiorespiratory arrest.[6]
- Some patients with dyspnoea or right heart failure have severe pulmonary hypertension due to silent recurrent PE (chronic thromboembolic pulmonary hypertension). This condition is probably a distinct disease entity, different from acute PE.

Prevention

See the separate Prevention of venous thromboembolism article.

Further reading

- British Thoracic Society Guideline for the initial outpatient management of pulmonary embolism (PE); British Thoracic Society (June 2018)
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