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<th>Pulmonary Thromboembolism (PE), Management of</th>
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<tr>
<td>AUTHOR</td>
<td>Dr Mark Newcombe</td>
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<td><a href="mailto:MARK.Newcombe@sesiahs.nsw.health.gov.au">MARK.Newcombe@sesiahs.nsw.health.gov.au</a></td>
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<td>KEY TERMS</td>
<td>Pulmonary Embolism</td>
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<td>SUMMARY</td>
<td>This guideline aims to provide an evidenced based safe and efficient approach to the management of Pulmonary Embolism.</td>
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Section 1 - Background

A. Epidemiology
Clinically relevant PE is uncommon as compared to pathological PE which is very common reflecting the normal role of the lung in filtering clot.

Historical inpatient autopsy data have greatly overestimated both incidence and mortality rates and have generally been unrepresentative of patients presenting to an emergency department. (1 / 2 / 3)

Of those being routinely tested for PE in an ED setting only 6-9% are found to have the diagnosis. (4 / 5)

This is compared to an incidence in inpatients which is much higher at 25-30%. (6 / 7)

Overall mortality is less than 5% and only 2-3% in those who are haemodynamically and echocardiographically stable. (8)

Treatment of confirmed PE will result in improved outcomes with complete resolution of perfusion defects occurs in 2/3 of patients and with a drastic reduction in short term recurrence. (9 / 10 / 11 / 12 / 13)

Given the vagaries of the pathology and epidemiology of PE unless there is a rigid evidence based process for the evaluation of those with potential PE we are unlikely to be able to maximise the risk-benefit ratio of our approach to this disease, under treating some and over treating many. (14)

B. Deciding Who Enters the Pathway
A combination of risk factors, symptoms, signs and investigation findings discovered on initial evaluation may prompt entry into the pathway for definitive evaluation.

None of these factors alone allow for exclusion or confirmation of the diagnosis.

Classic Thromboembolism risk factors include
- Recent Major Trauma especially lower limb fracture and spinal injury
- Known Hypercoagulable states
- Oestrogen Use
- Older age (esp those > 80)
- Malignancy
- Obesity
- Pregnancy
- Recent Surgery (especially orthopaedic and major general surgery)
- Immobilisation
- Prior Deep Venous Thrombosis (DVT) and PE (4 / 15)
Symptoms which may prompt further evaluation include
- dyspnoea especially if unexplained
- Chest pain especially if pleuritic
- Haemoptysis
- Syncope
(4)

The classic triad of dyspnoea, pleuritic chest pain, haemoptysis occurs in less than 20% of confirmed PE.
(16)

Signs which may prompt further evaluation include
- tachypnoea
- tachycardia
- signs of DVT
- hypoxia
(5)

C. Initial Investigations
If the diagnosis is considered then an ECG, Chest X-ray (CXR) and Blood Gas should be performed as part of the workup.

Whilst there are classical or eponymous findings on these tests they are neither specific nor sensitive enough to confirm or exclude a diagnosis of PE.

These tests however, may provide an alternative diagnosis, and can influence your assessment of the clinical probability.

The main use of CXR is in determining which more advanced radiological test the patient can proceed to, as the patient with an abnormal CXR is more likely to have a non diagnostic Ventilation Perfusion (VQ) scan than those with a normal CXR.
(17)

As such an abnormal CXR should prompt consideration of CT Pulmonary Angiogram (CTPA) as the next radiological form of management rather than VQ if further testing is required.

D. Diagnostic Pathways
For those patients where PE is a possible diagnosis then assessment through a structured pathway will provide for the best opportunity for a good patient outcome.

Whilst clinician gestalt assessment of the pretest probability for PE has been found to be equivalent to most scoring systems the clinicians evaluated were senior physicians and not all practitioners in the ED will fit into this group.

Components of a PE diagnostic pathway include the Pulmonary Embolus Rule out Criteria (PERC), the Wells score of pretest probability, d-dimer, VQ scan and CTPA, with accessory tests including Doppler venous ultrasound and echocardiography.
E. Pulmonary Embolus Rule out Criteria (PERC)

In those patients entered into a PE assessment pathway based on suspicious risk factors, symptoms, and signs this rule can be applied to rule out very low risk patients.

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<td>Pulse &lt; 100</td>
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<tr>
<td>SaO2 &gt; 94%</td>
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<tr>
<td>No Unilateral Leg Swelling</td>
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<tr>
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The prevalence of PE in those who were very low risk via clinical gestalt or are < 2 on a Wells score and met all the features was between 1.4 and 1.8% which is below the test threshold for an evaluation with d-dimer and advanced radiology (4 / 18 / 19).

This means that if patients in this group are tested aggressively the risk of doing harm with radiation, allergic reactions, contrast nephropathy and inappropriate anticoagulation greatly outweighs the benefit.

F. Wells Pretest Probability Scoring

Multiple different scoring systems rate approximately equally, in terms of accuracy, to the gestalt of an experienced clinician.

For the clinician with less than 10 years of experience then the use of a pretest probability scoring system provides a more reliable system wide approach.

The Wells score is the most studied and validated tool, including validation in the ED setting.

Entry into the use of the Wells is governed by our impression of the entire clinical picture along with contributing evidence from tests such as the Blood Gas, ECG and CXR which on their own will not allow a sensitive diagnosis.
The Wells Score

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<td>• PE is most likely diagnosis</td>
<td>+ 3</td>
</tr>
<tr>
<td><strong>Predisposing Factors</strong></td>
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<td>• Previous DVT or PE</td>
<td>+ 1.5</td>
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<td>• Recent Surgery or immobilisation (within the last 30 days)</td>
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<tr>
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<td>• Clinical signs of DVT</td>
<td>+ 3</td>
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(20)

**G. Categorisation of the Wells Score**

Categorisation of the wells score has traditionally been divided into 3 categories of probability
- Low Clinical Probability 0-1 points
- Intermediate Probability 2-6 points
- High Probability >= 7 points

The incidence of PE in these groups is
- Low 1.3% in ED pop 10% in inpatients
- Inter 16.2% in ED 20% in inpatients
- High 37.5% in ED 65% in inpatients

A dichotomous rule dividing probability scoring into unlikely and likely is also used
- PE unlikely 0-4 points
- PE likely > 4 points

Both schemes have been extensively validated and the overall miss rate of their use in combination with d dimer and advanced radiology is around 0.5%

**H. D Dimer**

The d dimer is a measure of the degradation product of cross linked fibrin.

This product is elevated in the presence of acute clot because of simultaneous coagulation and Fibrinolysis.
It is also elevated in the presence of a number of other processes such as cancer, inflammation, infection and necrosis.

A normal d dimer means acute clot is unlikely but an elevated d dimer can represent a number of conditions including acute clot.

As such it is a good test to be used where sensitivity is required.

The particular d dimer analysis used in ISLHN is the STA-Liatest, which is a latex agglutination quantitative determination by the immunoturbidimetric method.

At a cut off of 0.4 mg/L there is a 100% sensitivity allowing categorization as a high sensitivity test similar to the ELISA tests used in other health services.

I. Combining Pretest Probability Scoring and D Dimer

Measurement of the d dimer should only be used if the clinical probability is assessed first.

Traditionally d dimer has been used in the trichotomous allied to the low probability group with a negative d dimer in this group effectively ruling out PE in this group.

The 3 month risk of Thromboembolism in this group is less than 1%.

When using the dichotomous clinical prediction rule a negative D-dimer result is able to exclude PE safely in PE-unlikely patients.

J. Ventilation Perfusion Nuclear Medicine (VQ) Scanning

The VQ scan uses intravenous injection of Technetium 99m (Tc99m) labelled macro aggregated albumin particles to assess perfusion with poorly perfused areas appearing cold on scan, and TC99m and Xenon 133 (Xe133) tracers are given by inhalation with poorly ventilated areas appearing cold on scan.

Pulmonary Embolism is classically an area of normal ventilation and cold perfusion

The radiation delivered by VQ scan is as follows
- V- 0.3 mSv (15 CXRs / 7 weeks of background radiation)
- Q- 1.0 mSv (50 CXRs / 6 months of background radiation)

The advantages of VQ scanning are that there is less radiation exposure than CTPA, especially to the breast, less contrast related allergy and nephropathy than CTPA, and a high accuracy if used in the appropriate clinical setting.

The disadvantages of VQ scanning are that it is time consuming, it does not evaluate for alternate pathology, and it has limited availability in ISLHN (TWH only).
Reliable Results include the following
- Normal scan = no PE
- High Probability scan = PE
- Low Probability scan + low Pre Test Probability (PTP) = no PE
(33 / 34 / 35 / 36)

Unreliable Results requiring further testing include the following
- Low Probability scan + high PTP
- Intermediate Probability

K. Computed Tomography Pulmonary Angiogram (CTPA)
CTPA involves the delivery of timed IV contrast to allow direct radiographic evaluation of the pulmonary vasculature.

The radiation delivered by CTPA is 8 mSv (400 CXRs / 3.6 years of background radiation)
(30/31)

The advantages of CTPA are its high sensitivity (83-5%) and specificity (90-96%) when used in the appropriate clinical setting, its rapidity and availability (all centres except Bulli and MUH), and the ability to discover alternate findings requiring a change in management in 10-20% of patients undergoing the test.
(37 / 38 / 39 / 40)

The disadvantages of CTPA are the radiation risk, especially to breast tissue, the risk of Contrast Induced Nephropathy (CIN) of 10% (CIN defined as a rise in Creatinine by 25% within 3 days if IV contrast admin in the absence of other aetiology), and the rare risk of other contrast reactions such as allergy (minor reactions in 3%, anaphylaxis in 1/25000 injections and fatality in 1/170,000), contrast induced thyrotoxicosis and contrast extravasation. (Please note that there is no proven foetal or newborn effects from contrast delivered during pregnancy or during the lactation period).
(41 / 42 / 43 / 44 / 45)

Reliable Results include the following
- Negative CT in those with low PTP
- Positive CT in those with high PTP
(6)

Unreliable Results requiring further testing include the following
- Negative test in those with high PTP
(6)

L. Ultrasonography
Ultrasonography can involve bedside Emergency Physician (EP) B Mode (2D) compression Ultrasonography or formal radiology departmental ultrasonographer duplex (B Mode + Doppler) Ultrasonography.
Both allow detection of DVT which can be used to suggest PE in patients where definitive testing is difficult such as in the haemodynamically unstable patient and the pregnant patient.

The advantages of ultrasound is that the test is non invasive, cheap, widely available, and portable with no radiation load.

It is also reliably performed by trained EPs or departmental ultrasonographers.

The main disadvantage is that the absence of DVT does not rule out PE in those with a high pretest probability.

Ultrasound is also poor at detecting DVT’s below the knee and in the pelvis.

Discovery of a proximal DVT in those with a high pretest probability for PE has a specificity comparable to CTPA and in certain patients (haemodynamically unstable / pregnant) this combination may negate the need for further testing.

M. Trans Thoracic Echocardiogram (TTE)

Bedside TTE by the ED physician or echocardiographer observing for surrogate findings of PE is useful in the haemodynamically unstable patient where other diagnostic options are difficult.

Findings of right ventricular dysfunction such as RV dilatation, hypokinesia, altered contractility, altered ejection, or tricuspid regurgitation can allow a surrogate diagnosis of PE to be made in this unstable group.

It is however, poorly sensitive and a normal TTE does not exclude PE.

N. Treatment Options

The overall treatment aims in the management of PE include maintenance of cardiorespiratory stability, restoration of flow through the occluded pulmonary arteries, prevention of recurrence, and maintenance of normal lung function.

Initial Stabilisation

Treatment options specific to PE include
- airway control if required (rarely needed)
- provision of oxygen
- provision of ventilatory support
- rhythm control
- volume resuscitation if hypotensive
- if inotropic support is required then adrenaline is the preferred agent

(6 / 36 / 47 / 48 / 49 / 50 / 51 / 52)
There are multiple heroic measures considered in the literature including nitric oxide, inhaled prostacyclins, levosimendan, endothelin antagonists, phosphodiesterase inhibitors and surgical and percutaneous embolectomy. None of these are routinely available. The only heroic measure routinely available is ECMO and this would require early involvement of the Aeromedical Operations Centre (AOC) to discuss the potential patient transfer to an ECMO capable centre prior to commencement of this therapy.

Specific Treatments

Thrombolysis
Thrombolysis is indicated in the patient who is unstable, with instability defined as:
- hypoperfusion - SBP < 100 or relative drop of 60
- ventilator dependency
- cardiac arrest (usually PEA)

In this group of patients thrombolysis significantly reduces mortality and this benefit far outweighs the risk of harm from thrombolysis related haemorrhage.

Routine use in non high risk patients is not recommended as the risk benefit relationship is no longer favourable.

The difficulty in this group is making the diagnosis of PE and as discussed this is where bedside TTE and Ultrasonography can assist.

Heparin
Consensus on the use of heparin to prevent death and recurrent events has existed since the 1960s but actually good evidence for its use in Thromboembolism is lacking. It is generally recommended for use in those with confirmed PE and in those with a high pretest probability awaiting workup.

Low molecular weight heparin is the preferred option unless there is a high risk of bleeding or renal dysfunction as it has less side effects and similar efficacy to unfractionated heparin.

Venous Filters
Insertion of venous filters results in a reduced rate of PE and death where there is a known DVT in the first 2 weeks but there is no difference in mortality at 2 years.

There is however a high complication rate, including a substantial rate of IVC occlusion, so this mode is probably useful only where anticoagulation is a very risky such as after major surgery or in late pregnancy.
O. PE in Pregnancy

Pulmonary embolus in pregnancy remains the leading cause of pregnancy related death in the developed world with a 4-5 fold increased risk of PE during pregnancy compared to the non pregnant patient.

Diagnostic Process in Pregnancy

There are some differences in the diagnostic process because of the higher incidence of PE and concern regarding radiation exposure to young females.

Foetal radiation exposure is important but actually doesn’t impact greatly on the imperatives of the diagnostic process.

The main difference in the process is that the PERC rule is not advocated as the baseline risk of the diagnosis is too elevated.

The use of the d dimer and Wells score remains a valid method.

Physiological changes in pregnancy result in an altered coagulation profile but 50% of pregnant women will still have normal d dimer levels.

So a normal d dimer in a low pre test probability patient will still allow that patient to have PE ruled out.

A positive d dimer or a high pre test probability requires further radiological evaluation.

Radiological Testing

Once a patient is determined to require radiological testing the same options are available as in the non pregnant patient.

The main concern with these options is the degree of radiation exposure that are entailed with VQ and CTPA for young females.

The advantage of the lower limb ultrasound is that there is no radiation load.

If there is a proximal DVT in a high PTP patient it is legitimate to consider commencement of therapy without proceeding to other testing.

Similarly echocardiography is safe and remains part of the workup for the unstable pregnant patient with suspected PE.

The issues with radiation are twofold.

Radiation exposure to the foetus whilst not ideal is probably not going to alter the pathways greatly as the risk to the foetus is far outweighed by the risk of the disease.

This is only the case if a routine regularized consensus approach is used.

The absorbed radiation doses to the foetus for both VQ and CTPA is far below the 50mSv which is the upper dangerous limit for foetal injury by a factor of nearly 100.
Radiation doses to foetus (mSv)
16 slice ctpa
- 1st trimester 0.61-0.66
- 2nd NA
- 3rd 0.06-0.23

V
- 1st- 0.008
- 2nd- 0.01
- 3rd- 0.02

Q
- 1st- 0.48
- 2nd- 0.55
- 3rd- 0.46

Similarly the increased rate of childhood cancer from foetal exposure is 1:17000 per mSv (just over twice the background rate) is very low.

No adverse foetal effects due to contrast administration during pregnancy have been proven.

Current guidelines recommend that all neonates should receive thyroid function testing in the first week of life where the mother has received iodinated contrast material.

Cessation of breast feeding is not required given that the amount of contrast media excreted in breast milk is very small and the amount absorbed by the foetus is even smaller.

The taste of the breast milk is altered.

So the main issue with radiation exposure remains the potential effects on young females.

In terms of radiation dosage CTPA greatly exceeds VQ as previously described.

So the suggested technique for a workup is as follows:
- careful consideration as to whether the individual patient risk factors, symptoms, signs, and results of preliminary tests require entry into the PE pathway
- calculation of the Wells score
- d-dimer performed in the PE unlikely group with a negative result excluding the diagnosis and an elevated result requiring further workup
- Lower limb Doppler ultrasound with discovery of a DVT allowing treatment to be commenced without further testing whilst a negative result demands further evaluation
- VQ scanning with a reliable result allowing commencement of treatment or exclusion of the diagnosis and an indeterminate result requiring further evaluation
- CTPA if VQ produces an indeterminate result
This process will hopefully reduce over and under diagnosis and treatment and minimize radiation delivery to a population of young healthy female patients.

**Specific Treatment**

Pregnancy does have significant implications for the management options.

The risk of bleeding with thrombolysis is eclipsed by mortality rates in those patients where consensus demands thrombolysis and so it must be considered in the unstable group.

In this unstable group surgical embolectomy should be considered if close to delivery although the availability of this service is limited.

In terms of anticoagulation heparin remains the only option as warfarin is embryopathic in the 1st trimester, can cause foetal or neonatal haemorrhage in the 2nd and 3rd trimesters, and can cause CNS abnormalities during all trimesters.

Neither unfractionated nor low molecular weight heparin crosses the placenta or enters the breast milk so either form can be used.

Some form of heparin will be required for the remainder of the pregnancy.

If an epidural is required then cessation of heparin for 12 hours before and 12-24 hours after the procedure is required.

After delivery commencement of warfarin can occur and continue for a minimum of 3 months.
Section 2 – Pulmonary Thromboembolism (PE) Evaluation Pathway

A. Step 1: Pathway Entry
Patients with suspicious symptoms, signs and risk factors can be considered to enter the pathway.
Discussion with a staff specialist or registrar should precede entry into the PE pathway.

Symptoms to consider
- Dyspnoea (especially if unexplained)
- Chest pain (especially if pleuritic)
- Haemoptysis
- Syncope

Signs to consider
- Tachypnoea
- Tachycardia
- Signs of DVT
- Hypoxia

Risk Factors to consider
- Recent major trauma
- Recent immobility
- Recent surgery
- Hypercoagulable states
- Obesity
- Active malignancy
- Pregnancy
- Oestrogen use
- Prior DVT/PE
- > 80 years of age

B. Step 2: Is the Patient Stable?
Triage and Initial Stabilisation focusing on respiratory and circulatory stability

Airway
Rarely an issue
Patency, Protection or ventilation requirements would be treated in a standard fashion

Breathing
Standard Assessment of Respiratory Rate, Oxygen Saturations and Respiratory Work
Provision of Supplemental Oxygen
Consider Respiratory Support with Non Invasive or Invasive Ventilation as required
Circulation
Standard Assessment of Pulse, Blood Pressure, and Capillary Refill
→ Instability in PE is SBP < 90 or a Pressure Drop of >= 40 for > 15 mins in the absence of another cause
Early ECG + Monitoring if Unstable
Establishment of IV access
Consider Circulatory support with Volume Resuscitation, Rhythm Control and Adrenaline if inotropic support is required

Consideration of other Life-Threatening diagnoses with similar symptoms
- ACS
- Aortic Dissection
- Tension PTX
- Oesophageal Rupture
- Pancreatitis
- Ectopic Pregnancy
- AAA

Specific Management in the Unstable PE patient
Consider
→ immediate IV heparinisation
→ bedside Trans Thoracic Echocardiography (TTE) and Lower Limb Ultrasonography
   - presence of RV dysfunction or proximal DVT may aid diagnosis
→ Thrombolysis- rtPA / Alteplase 0.6 mg/Kg (max 50mg) over 15 mins

The only heroic addition to treatment available locally would be ECMO. A decision on this therapy will be made at consultant level with assistance from the Aeromedical Operations Centre.

C. Step 3: Detailed Initial Assessment
In the stable patient a thorough assessment is the next step including
Detailed History
Detailed Examination
ECG
CXR
+/− V/ABG

This assessment will not allow a definitive diagnosis but will influence your assessment of probability of the diagnosis of PE.
If an alternative diagnosis is made at this time then the further steps down the pathway can be curtailed.
D. Step 4: The Pulmonary Embolism Rule out Criteria (PERC)
In those with typical symptom(s) but very low risk apply the PERC

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If there is a very low clinical suspicion and the patient fits all eight criteria then the probability of PE is low and **NO** further testing is required. Skip this step in Pregnancy.

E. Step 5: Determine the Pre-Test Probability (PTP) of PE using the Wells Score

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<thead>
<tr>
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</table>

Interpretation

<table>
<thead>
<tr>
<th>Clinical Probability</th>
</tr>
</thead>
<tbody>
<tr>
<td>PE Unlikely</td>
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<tr>
<td>PE Likely</td>
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F. Step 6: Perform d dimer on PE unlikely group
Negative d dimer → **NO PE** → Look for alternate diagnosis
Positive d dimer → Radiological test required
G. Step 7: Perform Appropriate Radiological test on positive d dimer group and PE likely group
(consider treatment as per step 9 prior to test if patient in PE likely group)

**VQ** chosen if
Normal CXR and absence of known structural lung disease
< 55 yo
Renal dysfunction
No alternate diagnosis requiring CT rule out
Test available
**Interpretation**
normal scan = No PE → consider alternate diagnosis
low probability scan + low PTP = No PE → consider alternate diagnosis
   + high PTP = further testing required
intermediate prob = further testing required
high prob = PE → commence treatment

**CTPA** chosen if
Abnormal CXR or known structural lung disease
> 55 yo
alternate diagnosis requiring CT
VQ not available
**Interpretation**
alternate diagnosis discovered → treat
negative + low PTP = No PE
negative + high PTP = further testing required
positive + low PTP = treat but further testing reqd (15% false pos)
positive + high PTP = PE

**Doppler Ultrasound** of both Legs chosen if
Patient Pregnant
VQ and CTPA contraindicated
**Interpretation**
above knee DVT in pregnant patient = PE
absence of above knee DVT = further testing required

**Further testing** can come in the form of the alternate radiological test to that already performed- US, VQ or CTPA.
Treatment decisions at this point will be made at consultant level.

H. Step 8: Treatment
PE Confirmed
→ admission
   heparinisation
   - Enoxaparin in those with normal renal function
   - UFH in those with abnormal renal function
Vascular review for consideration of Greenfield filter if
- high proximal DVT
- very high risk from heparinisation (late pregnancy / post major surgery)
Supportive care
- analgesia
- compression stockings

Tests inconclusive but patient high PTP
→ discuss with Respiratory Physician

PE Excluded
→ ongoing investigation until there is an alternate explanation for patients' presentation
A. Variations in Pregnancy

The pathway remains the same apart from skipping step 4 (PERC) and using a lower limb Doppler ultrasound as the initial radiological test of choice. If this is positive then treatment can commence. If the ultrasound is negative then a radiological test can be chosen in the standard fashion with VQ preferred to reduce radiation exposure to the breast tissue.
B. PE Evaluation Summary

1. Pathway Entry
2. Patient Stable?
3. Assessment
4. PERC
5. Wells
6. d dimer
7. Radiology
8. Treatment
Section 4 – References


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Aust NZ J Obstet Gynaecol 2004;44:452


**Revision and Approval History**

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