PULMONARY EMBOLISM (PE): DIAGNOSIS AND TREATMENT

OBJECTIVE:
To provide a diagnostic algorithm and treatment options for patients with acute pulmonary embolism (PE).

BACKGROUND:
Venous thromboembolism (VTE) is a common disease, affecting approximately 1-2 in 1,000 adults per year. Approximately one third of first VTE presentations are due to PE while the remainder are due to deep vein thrombosis (DVT). The incidence of PE has increased significantly since the advent of computed tomography (CT) angiography due to its widespread availability and diagnostic sensitivity. The majority of PEs originate in the proximal deep veins of the leg, despite the fact that only 25-50% of patients with PE have clinically-evident DVT. Active malignancy, surgery (especially orthopedic), immobilization >8 hours, and estrogen use/pregnancy are transient provoking factors. Up to 50% of first-time PEs are unprovoked.

Symptoms of PE may include sudden onset dyspnea, pleuritic chest pain and syncope. Signs of PE may include tachypnea, tachycardia, hypoxemia, hypotension, and features of right ventricular dysfunction (distended jugular veins). The ECG may show right ventricular strain (S1Q3T3, right bundle branch block and T-inversion in leads V1-V4).

Up to 10% of symptomatic PEs are fatal within the first hour of symptoms. Independent predictors of early mortality include hypotension (systolic blood pressure ≤90 mmHg), clinical right heart failure, right ventricular dilatation on CT/echocardiography, positive troponin, and elevated brain natriuretic peptide (BNP). Early diagnosis and treatment of PE reduces morbidity and mortality.

DIAGNOSIS OF PE:
The constellation of symptoms and signs of PE may be suggestive, but do not alone have the sensitivity or specificity to rule in or rule out the diagnosis. When the diagnosis of PE is considered, the clinical stability of the patient and their pre-test probability will dictate the diagnostic approach (see Figure 1).
**FIGURE 1: SUGGESTED DIAGNOSTIC ALGORITHM FOR SUSPECTED PULMONARY EMBOLISM**

* Consideration for thrombolysis without diagnostic test confirmation should be made if the patient is very unstable or moribund

** Features on echocardiography suggestive of massive PE include RV overload and RV/pulmonary artery thrombus

*** If patient condition stabilizes, consideration for CTPA should be given to confirm diagnosis

**** Excluding a diagnosis of PE with a moderate pre-test probability requires the use of a highly sensitive d-dimer assay. The use of age-specific D-dimer cut-off values, if available, appear to improve the specificity of D-dimer testing.

In patients without hypotension (SBP ≥90 mmHg), pre-test probability should be assessed by experienced clinician ‘gestalt’ or a validated clinical prediction rule (see Table 1). In cases with low to intermediate clinical probability, a negative D-dimer result rules out the diagnosis of PE. However, a positive D-dimer test must be followed up with a definitive test to confirm/refute the diagnosis of PE. Multidetector CT pulmonary angiography (CTPA) is widely available in Canada, and is sufficiently sensitive and specific to exclude the diagnosis of PE when it is negative and to confirm it when positive.

**TABLE 1: WELLS SCORE* FOR PE**

<table>
<thead>
<tr>
<th>VARIABLE</th>
<th>POINTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical symptoms and signs of DVT</td>
<td>3</td>
</tr>
<tr>
<td>Previous DVT or PE</td>
<td>1.5</td>
</tr>
<tr>
<td>Immobilization for &gt;3 days or surgery within 4 weeks</td>
<td>1.5</td>
</tr>
<tr>
<td>Heart rate &gt;100 beats/minute</td>
<td>1.5</td>
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</table>
In patients with low clinical probability of PE, and in the absence of D-dimer testing, the diagnosis of PE can be safely excluded if NONE of the following are present: age >50, prior VTE, surgery or trauma past 4 weeks, current exogenous estrogen use, hemoptysis, heart rate >100, oxygen saturation <94%, or unilateral leg swelling.

With a **high pre-test probability**, there is no value in ordering D-dimer, as the post-test probability of a negative D-dimer result remains unacceptably high. Therefore, when the pre-test probability is high, one should go directly to CTPA to establish the diagnosis.

In patients with **renal failure** or an **allergy to contrast dye** (in whom a CTPA is felt to be contraindicated), it is reasonable to start with lower extremity compression ultrasound (CUS) looking for evidence of DVT. A positive result will mandate the same treatment as for PE; therefore, no further investigations for PE are required. Since up to 30% of patients may not have concurrent DVT with PE, a negative CUS does not rule out PE. Therefore, a ventilation-perfusion (V/Q) scan should be obtained in this instance.

In patients with hypotension who are too unstable to undergo CTPA, or if CTPA is not immediately available, an urgent echocardiogram should be obtained to look for evidence of embolus in the RV or pulmonary arteries, or right heart overload. If present, and in the absence of an alternative diagnosis, treatment for PE should be initiated. However, RV dysfunction alone does not prove PE; therefore, if feasible, confirmatory evidence of VTE should be sought with CTPA or CUS. If a hypotensive patient does not have echocardiographic features of RV dysfunction, it is unlikely that their hemodynamic instability is due to massive PE (although this does not exclude smaller PE).

**TREATMENT OF PE:**

Patients who have a high pre-test probability of having PE should be initiated promptly on anticoagulant therapy. Treatment can be withheld in patients with intermediate and low pre-test probabilities of PE, assuming definitive diagnostic testing will be completed within 4 or 24 hours, respectively. All patients with confirmed PE should be risk-stratified to determine whether they require in-hospital treatment or if outpatient management is sufficient [see the PESI and Simplified PESI risk models in the Thrombosis Canada Clinical Tools]. Patients presenting with hypotension (SBP ≤90 mmHg or a 40 mmHg drop from baseline) that is not responsive to a small fluid challenge or due to another cause (e.g. tachycardia) carry a 15% risk of early mortality and should be admitted. Patients who are clinically well and do not have evidence of myocardial injury or RV dysfunction are at low risk for early mortality (<1%) and may be appropriate for early discharge or home treatment.

Options for initial treatment include unfractionated heparin (UFH) or low molecular weight heparin (LMWH) bridge to therapeutic warfarin, initial LMWH followed by a novel oral anticoagulant (NOAC),

<table>
<thead>
<tr>
<th>Hemoptysis</th>
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<tr>
<td>Malignancy</td>
<td>1</td>
</tr>
<tr>
<td>No alternative diagnosis more likely than PE</td>
<td>3</td>
</tr>
</tbody>
</table>

*Total Score: Low Risk: 0 to 1.5; Intermediate Risk: 2 to 5.5; High Risk: ≥ 6*
or NOAC monotherapy. Regardless of mechanism, anticoagulation should be continued for at least 3 months [see Venous Thromboembolism: Duration of Treatment guide].

ANTICOAGULANT AGENTS AND DOSING:

Low molecular weight heparin
LMWH may be used as initial therapy in conjunction with warfarin or may be used as monotherapy for the full duration of treatment (the preferred acute and long-term treatment for cancer patients). Most patients have little difficulty with LMWH self-administration. LMWH offers advantages over UFH, including better bioavailability when administered subcutaneously, longer duration of anticoagulant effect often enabling once daily treatment, lower risk of heparin-induced thrombocytopenia (HIT), predictable anticoagulant effect allowing fixed dosing based on body weight and renal function, less effect on bone metabolism, and no requirement for laboratory monitoring.

Dalteparin (Fragmin®): 200 U/kg subcutaneously (SC) once daily or 100 U/kg SC twice daily (once daily dosing is generally preferred).
Enoxaparin (Lovenox®): 1 mg/kg SC twice daily or 1.5 mg/kg SC once daily.
Tinzaparin (Innohep®): 175 U/kg SC once daily.

For patients with severe renal insufficiency (creatinine clearance [CrCl] <30 mL/min), clinical data on the use of LMWH for the treatment of PE are limited and LMWHs should generally be avoided. If used, the dose of LMWH should be reduced and monitoring with anti-factor Xa levels is suggested.

Unfractionated heparin
UFH use in the treatment of PE is limited by a narrow therapeutic range, inter-individual variation in anticoagulant effect, need for laboratory monitoring, and increased risk of HIT. The use of UFH should be limited to: (1) patients with severe renal insufficiency (CrCl <30 mL/min), in whom LMWHs and NOACs should be avoided; (2) patients at high risk for bleeding, in whom rapid reversal of the anticoagulant effect may be needed; and (3) patients who receive thrombolytic therapy. Intravenous UFH is generally started with a bolus of 5,000 U (or 80 U/kg) followed by a continuous infusion starting at 20 U/kg/hr. The target activated partial thromboplastin time (aPTT) range is defined by the local hospital laboratory and is generally 2-3 times the baseline value.

Thrombolysis
In most patients with PE, the risk of major bleeding with intravenous thrombolysis outweighs the benefit, except in some patients who present with massive PE. Massive PE is defined as anatomically extensive PE plus persistent hypotension or overt right heart failure, where the short-term mortality is >15%. Therefore, IV thrombolysis should be reserved for patients with persistent hypotension (SBP <90 mmHg or a 40 mmHg drop from baseline) refractory to a small fluid challenge or clinical right heart failure and who do not have a contraindication. Thrombolysis is NOT indicated in submassive PE (normotensive with right ventricular dysfunction) as it increases major bleeding and stroke without survival benefit. Thrombolysis is given as follows: recombinant tissue plasminogen activator (rt-PA) 100 mg over 2 hours or 0.6 mg/kg as a bolus; or weight-adjusted tenectaplaste (TNK) as a bolus. Intravenous UFH should be used initially after thrombolytic therapy, followed by anticoagulation with warfarin or a NOAC.
**Warfarin**

Initial treatment with warfarin should be combined with an immediate-acting agent such as LMWH for at least 5 days and until INR is at least 2.0 for at least two days. As warfarin takes several days to take effect, warfarin monotherapy is not an acceptable treatment option. Initial dosing is typically 5 mg once daily, but the therapeutic dose is highly variable. The elderly, infirm and those with low body-weight typically require a lower dose; initial dosing with 2-3 mg should be considered. Conversely, relatively young, healthy and large patients typically require a higher dose; initial dosing with 7.5-10 mg should be considered. Frequent monitoring is required until a stable, in-range INR is reached, after which testing every 2-6 weeks is usually adequate. Warfarin is associated with many drug and food interactions that affect the INR. Alterations in concomitant medications and new concurrent illness should lead to INR testing. Patients should not be encouraged to reduce intake of foods high in vitamin K, but to maintain a consistent, balanced diet.

**Dabigatran (Pradaxa®), Rivaroxaban (Xarelto®), Apixaban (Eliquis®):**

Large phase 3 studies have demonstrated the efficacy and safety of these agents for the initial (rivaroxaban, apixaban), acute (all agents) and extended (all agents) treatment of PE. All three agents have been approved in Canada for the treatment of patients with PE. An initial course of LMWH is not required with rivaroxaban and apixaban. The recommended dose of rivaroxaban is 15 mg twice daily for the first 21 days, followed by 20 mg once daily for the duration of treatment, which should be at least 3 months. The recommended dose of apixaban is 10 mg twice daily for the first 7 days, followed by 5 mg twice daily. In keeping with trial design and recommendations, five days of therapeutic LMWH should be administered prior to the initiation of dabigatran when this anticoagulant is used for the treatment of VTE.

**SPECIAL CONSIDERATIONS:**

**Catheter-directed thrombolysis for massive PE**

In some hospitals where there is requisite expertise, catheter-directed thrombolysis may be considered since it is able to deliver a thrombolytic agent directly into one or more large emboli and can rapidly relieve pulmonary artery occlusion with minimal risk of bleeding. Such treatment should be undertaken in consultation with a specialist.

**Chronic thromboembolic pulmonary hypertension (CTEPH)**

CTEPH develops in up to 3% of patients after an episode of PE. Patients with CTEPH should be given long-term anticoagulation to prevent recurrent PE. Pulmonary thromboendarterectomy often reduces pulmonary pressures and symptoms of pulmonary hypertension, although mortality for such surgery is about 5% even in the most experienced centres.

**Patients contraindicated for anticoagulation**

See Vena Cava Filter guide.

**Pregnancy**

See Pregnancy: Venous Thromboembolism Treatment guide

**Cancer**

See Cancer and Thrombosis guide.
**Pediatrics**
The diagnosis of PE in children should always be confirmed with a V/Q scan, CT with contrast or magnetic resonance imaging (MRI). Treatment may be initiated with either age-appropriate UFH or LMWH followed by 3 months (for a provoked VTE) or longer-term anticoagulation for recurrent or unprovoked events using either LMWH or warfarin. [See Pediatric Thrombosis guide]

**OTHER RELEVANT GUIDES:**
- Apixaban (Eliquis®)
- Cancer and Thrombosis
- Dabigatran (Pradaxa®)
- Deep Vein Thrombosis (DVT): Diagnosis
- Deep Vein Thrombosis (DVT): Treatment
- Pregnancy: Venous Thromboembolism Treatment
- Rivaroxaban (Xarelto®)
- Unfractionated Heparin and Low-molecular-weight Heparin
- Vena Cava Filter
- Venous Thromboembolism: Duration of Treatment
- Warfarin

**REFERENCES:**


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*Please note that the information contained herein is not to be interpreted as an alternative to medical advice from your doctor or other professional healthcare provider. If you have any specific questions about any medical matter, you should consult your doctor or other professional healthcare providers, and as such you should never delay seeking medical advice, disregard medical advice or discontinue medical treatment because of the information contained herein.*