Pulmonary Embolism

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Faculty

Dalia Saha, MD, is a board-certified internal medicine physician with more than 15 years of clinical experience. With experience in both academic and private healthcare settings, Dr. Saha has vast exposure to many aspects of patient care and clinical medicine. Always interested in the didactic component of health care, Dr. Saha works on the education committee for the American College of Physicians and is an instructor and teaching staff for medical students and residents in George Washington University and Johns Hopkins Medical Schools. Lauded by her colleagues for her dedication and work ethic in the field of medicine, she has been awarded the Top Doctor Award in Washington, DC.

Faculty Disclosure

Contributing faculty, Dalia Saha, MD, has disclosed no relevant financial relationship with any product manufacturer or service provider mentioned.

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The division planners and director have disclosed no relevant financial relationship with any product manufacturer or service provider mentioned.

Audience

This course is designed for physicians, PAs, and nurses involved in assessing, triaging, and managing patients with suspected pulmonary embolism.

Accreditations & Approvals

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Disclosure Statement

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Course Objective

The purpose of this course is to provide healthcare professionals with the knowledge and clinical strategies necessary to optimally triage and treatment patients with pulmonary embolism.

Learning Objectives

Upon completion of this course, you should be able to:

1. Define a thromboembolic event.
2. Explain pathogenesis, risk factors, and demographics of pulmonary embolism (PE).
3. Review the diagnostic workup of PE.
4. Compare the different types of PE treatments in both inpatient and outpatient settings.

EVIDENCE-BASED PRACTICE RECOMMENDATION

Sections marked with this symbol include evidence-based practice recommendations. The level of evidence and/or strength of recommendation, as provided by the evidence-based source, are also included so you may determine the validity or relevance of the information. These sections may be used in conjunction with the course material for better application to your daily practice.

INTRODUCTION

Pulmonary embolism (PE) is very common in both inpatient and outpatient settings [1; 2]. It should be one of the first considerations when a patient presents with acute-onset dyspnea, shortness of breath, and chest pain. Other common symptoms include cough, hemoptysis, diaphoresis, and feverishness.

A PE is an abrupt occlusion of the pulmonary artery and/or one of its branches. The occlusion may consist of blood clot/thrombus, air, fat, or malignancy/tumor originating in another part of the body, which dislodges and travels through the venous system to the right side of the heart and thence the pulmonary vasculature. In most cases, PE arises from deep vein thrombophlebitis in the lower legs or pelvis, following trauma, surgery, infection, or an acquired hypercoagulable state.

The natural history of PE is variable. PE may be single or multiple (pulmonary emboli), small and clinically silent, large or recurrent with progressive obliteration of the pulmonary vascular bed, causing cardiorespiratory failure. Symptomatic PE is commonly associated with significant morbidity and mortality risk; the challenge for clinical care providers is early recognition and prompt therapeutic intervention to relieve pulmonary artery obstruction and prevent additional pulmonary emboli, any one of which could prove fatal [1; 2]. With modern technology, which can detect small embolic events, the condition is identified much earlier, making possible effective treatment prior to complete hemodynamic collapse [1; 2; 3]. Assessment and prevention in outpatient settings have also led to improvements in mortality. Research indicates that small, subclinical pulmonary emboli probably occur with some frequency but are transient in nature and go unnoticed; however,when there is predisposition to venous stasis (e.g., inflammation, injury, heart failure, coagulopathy), single large or recurrent PE becomes a challenging clinical illness requiring prompt diagnosis and treatment.

Classification of PE typically categorizes the disease as hemodynamically stable or unstable. The most common type is hemodynamically stable, which can range from small, mildly symptomatic or asymptomatic PE (previously referred to as low-risk PE or small PE) to those who present with right ventricular dysfunction but who are hemodynamically stable (previously referred to as submassive or intermediate-risk PE) [3; 4]. While PE characterized by right ventricular dysfunction can be hemodynamically stable, more severe (unstable) disease is characterized by the presence of systemic arterial hypotension, which indicates at least half of the pulmonary vascular tree is affected [4; 5]. Hemodynamically unstable PE (previously referred to as massive or high-risk PE) will result in significant hypotension. Hemodynamic instability is defined as the presence of cardiac arrest requiring resuscitation, or obstructive shock or persistent hypotension not caused by other pathologies [36].

EPIDEMIOLOGY

The annual incidence of PE is difficult to pinpoint but is estimated to be about 60 to 70 cases per 100,000 population [6]. General autopsy studies from all-cause mortality have found PE, variable in number and age, to be present in 30% to 45% of cases [6; 7; 8; 9].

Behind only stroke and coronary artery disease, PE is one of the most common types of cardiovascular disease. It is more common in patients 60 to 70 years of age, with the highest incidence in patients 70 to 80 years of age. Although death following a diagnosis of PE is relatively common, as high as 30%, many of these patients have coexisting serious conditions, such as cancer, recent surgery, or sepsis. The direct mortality associated with undiagnosed/untreated PE during the course of diagnosis and treatment is about 5% to 8%. An estimated 10% of patients with acute PE die suddenly; approximately two-thirds of patients who die from PE do so within two hours of presentation. The mortality rate for those treated for hemodynamically unstable PE is about 20%, and

those with cardiogenic shock have a mortality rate of 25% to 30%. Those with a hemodynamically stable PE have a mortality rate of 1% to 25%, depending on the degree of right ventricular dysfunction [2; 4; 5; 10].

PATHOPHYSIOLOGY

Most commonly, a PE occurs when a deep vein thrombus detaches and migrates, or embolizes, into the pulmonary circulation. This can lead to blockage of the pulmonary vasculature, causing a ventilation-perfusion (VQ) mismatch and impairing gas exchange and circulation. PE is more common in the lower lung fields, compared with the upper ones, and both lungs are typically involved. Peripheral PE, as opposed to central PE, can lead to a pulmonary infarction coupled with alveolar hemorrhage. As further obstruction of the pulmonary artery occurs, there is an increase in dead space ventilation and elevation of pulmonary arterial pressure by increasing pulmonary vascular resistance. This further worsens VQ mismatch, with vascular occlusion of the arteries.

Various serum factors are released during a PE formation, including serotonin and thromboxane, which are produced from activated platelets [1; 2; 4]. This induces a cascade of hormonal triggers and related vasoconstriction. Pulmonary arterial pressure increases, which worsens right ventricular afterload and can lead to right ventricular failure and eventually left ventricular system failure. Further clinical progression will lead to a myocardial ischemia due to inadequate coronary circulatory flow, systemic hypotension, and eventual death [1; 4; 5].

DIAGNOSIS

A strict (confirmatory) diagnosis of PE would require direct anatomic evidence of pulmonary artery obstruction, which by modern imaging technique (e.g., computed tomography [CT] angiography) would involve invasive measures and exposure to radiation. As the size and distribution (severity) of PE are variable, the preferred strategy for selecting diagnostic testing relies on degree of clinical suspicion, clinical judgment, and assessment of pre-test probability. Selection of noninvasive testing to rule out the diagnosis, based on the assessed clinical probability of PE, has proved effective in reducing the use of CT imaging, thereby minimizing lung and breast-tissue exposure to irradiation [27]. The differential diagnosis includes heart failure, pneumothorax, pneumonia, sepsis, acute chest syndrome, chronic obstructive pulmonary disease (COPD) exacerbation, and anxiety or other psychotropic illnesses. A systematic review and meta-analysis found that a history of sudden dyspnea, syncope, thrombophlebitis, previous deep vein thrombosis, leg swelling, active cancer, or recent surgery was associated with an increased probability of PE [54]. An inability to increase alveolar oxygen pressure (PaO_2) greater than 8.0 kPa (60 mm Hg) despite high-flow oxygen should also raise suspicion for PE.

When a patient does not speak the same language as the clinician, a professional interpreter should be consulted to ensure accurate communication. A retrospective chart review found that, for non-English-speaking patients suspected of having sustained a PE, the positive diagnostic yield of pulmonary angiogram for those who requested an interpreter (7.37%) was nearly double that of those who did not request an interpreter (3.23%) [49].

DIAGNOSTIC WORKUP

Vital Signs

In initial evaluation, vital signs such as blood pressure, heart rate, and rapid estimation of oxygenation by pulse oximetry are critical to assessing severity of vascular compromise and the stability of the patient. Arterial blood gas (ABG) testing will confirm if a patient has hypoxemia and can be used to obtain the arterial-alveolar gradient to determine if there is a PE or other VQ mismatch [10; 11; 12; 13].

D-dimer Level

Assessment of D-dimer levels can be used for screening purposes and to rule out PE if the pretest probability is intermediate or low. D-dimer is a byproduct of intrinsic fibrinolysis. It is considered to be a highly sensitive test for the absence of PE and has a very high negative predictive value. A normal D-dimer level effectively rules out PE or deep vein thromboembolism. In the event that the d-dimer is elevated, further testing (e.g., computed tomography [CT] angiography, planar VQ scanning) can be performed [10; 14; 15; 16]. Because the test is not specific, an elevated finding is not diagnostic. The specificity of D-dimer decreases with age, and the use of age-adjusted cut-offs is recommended for patients older than 50 years of age. The formula is age (years) x 10 mcg/L for patients older than 50 years of age.

Cardiac Biomarkers

Cardiac biomarker testing may also be useful, particularly as it can identify other diagnoses (e.g., myocardial infarction) [10; 11; 17]. It may help identify signs of right ventricular strain and/or ischemia. An elevated brain natriuretic peptide (BNP) level may indicate right ventricular dysfunction, and higher levels correlate with greater severity of dysfunction.

Various cardiac troponins have also been assessed for diagnostic significance in patients with PE. While these measurements are not diagnostic, elevated troponin is significantly associated with higher mortality in patients with PE [18].

Imaging

Diagnostic imaging is indicated for patients in whom PE cannot be ruled out based on clinical assessment and noninvasive testing. For these patients, CT pulmonary angiography is usually an easily accessible diagnostic imaging modality. It is fast, accurate, and both specific and sensitive. It is also useful for identifying other lung pathology, such as pneumonia and effusions [15; 16]. However, it does require that the patient have good renal function due to the use of iodinated contrast, and it also entails lung and breast-tissue irradiation. Ventilation-perfusion single-photon-emission CT (VQ scan) is a low-radiation option to minimize radiation exposure in younger patients.

Chest x-ray is nonspecific but can help identify pleural effusions and diaphragmatic changes. The classic Westermark sign, which shows a clarified area (loss of vascular markings) distal to a large occluded vessel, and Hampton hump, a dome-shaped, pleural-based opacification, may be present on x-ray. These findings are strongly specific for PE (92% and 82%, respectively) but are not sensitive (14% and 22%, respectively). Chest x-ray can also assist in ruling out pneumonia as part of the differential.

VQ scans visualize areas that are ventilated but not perfused (i.e., VQ mismatch). This testing requires more time, is less specific than CT angiography, and should be done with clinical correlation. However, it is the imaging modality of choice for patients with suspected PE and normal chest x-ray for whom CT angiography is contraindicated, including those with impaired kidney function and pregnant patients. Normal ventilation is 4 L air/minute, and normal perfusion is 5 L blood/minute; thus, a normal VQ ratio is 0.8. A high VQ ratio (>0.8) indicates that the patient's ventilation is exceeding perfusion, while a low VQ ratio indicates a VQ mismatch caused by poor ventilation. When blood is diverted away from the occluded section, overperfusion can occur in the normally ventilated regions. The modified Prospective Investigation of Pulmonary Embolism Diagnosis (PIOPED-II) criteria score the probability of PE based on VQ scan findings (***Table 1***).

MODIFIED PROSPECTIVE INVESTIGATION OF PULMONARY EMBOLISM DIAGNOSIS (PIOPED-II) CRITERIA	
Probability of PE	**Criteria**
High probability	Two or more large mismatched segmental perfusion defects or the arithmetic equivalent of moderate and/or large defects
Normal perfusion or very low probability	No perfusion defects Nonsegmental perfusion defects without other perfusion defects in either lung Perfusion defects smaller than corresponding chest x-ray opacity One to three small subsegmental perfusion defects Two or more matched ventilation and perfusion defects with a regionally normal chest x-ray and some areas of normal perfusion elsewhere Solitary triple-matched defect in a single segment in the middle or upper lung zone Stripe sign Large pleural effusion without other perfusion defects in either lung
Low or intermediate probability	All other findings

Source: [19] *Table 1*

Duplex ultrasonography for detection of lower extremity venous thrombi is a useful noninvasive test to assess risk and probability in a patient suspected of having PE. It has both high sensitivity and specificity for thrombus [14; 20; 21; 22]. However, a negative test result does not rule out PE, as the thrombus may have dislodged and embolized prior to the testing.

Electrocardiogram

Electrocardiographic signs of right ventricle strain, such as T wave inversions in V1–V4, QR pattern in V1, the S1Q3T3 pattern, and incomplete or complete right bundle-branch block, are useful but insensitive for the assessment of right ventricle dysfunction in acute PE. However, the presence of right ventricular strain on electrocardiogram has been shown to correlate with the extent of pulmonary vascular obstruction and outcomes of acute PE [10; 11; 12; 14; 17; 24].

Echocardiogram

Echocardiography can demonstrate if there was a clot in the right atrium or ventricle and can also be used to show if there are signs of right ventricular dilatation and hypokinesis [12]. When performed, echocardiography has been shown to reduce other testing and lead to more aggressive early therapy [12; 22].

Pulmonary Arteriography

Pulmonary arteriography is a rare test typically performed only on patients with suspected PE for whom CT and chest x-ray are not feasible. It may also be used with cardiac catheterization to assess patients who have chronic thromboembolic pulmonary hypertension to determine if they are good candidates for pulmonary endarterectomy.

GENETIC TESTING

Factor V Leiden (FVL) and prothrombin (PT) genetic variants are associated with an increased risk of future venous thrombosis or PE. Genetic tests for FVL and PT variants are widely available and commonly used. One current use of these tests is to inform decisions regarding anticoagulant medication in order to decrease the risk of future clots (i.e., secondary prevention). The independent Evaluation of Genomic Applications in Practice and Prevention (EGAPP) Working Group found enough evidence to recommend against routine testing for FVL and PT gene variants in adults who have idiopathic venous thromboembolism, since longer term preventive treatment with anticoagulant medication offers similar benefits to patients whether or not they have these genetic variations. They also recommend against routine testing for adult family members who do not have a history or symptoms of venous

thromboembolism, when the testing is conducted to help decide whether to treat them preventively with anticoagulant medication [50]. However, for patients with venous thromboembolism associated with commonly recognized modifiable risk factors (e.g., contraceptive use, estrogen replacement), genetic testing may help guide preventive treatment decisions.

CLINICAL SCORING SYSTEMS

The Wells criteria (***Table 2***) and the PE Rule-Out Criteria (PERC) assist clinicians with determining clinical probability for PE [14]. One of the important criteria in the determination of PE is if there is a more likely alternate diagnosis, and this is somewhat subjective. If the Wells criteria are used, a score greater than 6 is considered high probability of PE, 2–6 is moderate probability, and less than 2 is low probability. A modification of the Wells criteria simplifies scoring to either likely (>4) or unlikely (≤4).

The PERC rule was developed for use in emergency care to rule-out PE in patients whose likelihood of PE is low (<15%), so unnecessary diagnostic workups can be avoided. The PERC rule includes [26]:

- Age younger than 50 years
- Heart rate less than 100 beats per minute
- Oxygen saturation of at least 95%
- No prior deep vein thrombosis or PE
- No unilateral leg swelling
- No hormonal estrogen use
- No hemoptysis
- No history of surgery or trauma requiring prior hospitalization in the previous four weeks

If all eight criteria are fulfilled, the patient's risk for PE can be considered sufficiently low and further testing is not necessary [10; 11; 13; 17]. In practice, clinicians tend to overestimate the probability of PE. In cases in which the clinician judges that the patient is very unlikely to have PE but is uncertain whether the estimated likelihood is <15%, the PERC rule or Wells score ≤4 in combination with a normal D-dimer level is reassuring and can be used to safely rule out PE.

WELLS CRITERIA	
Clinical Features	**Points**
Clinical symptoms of deep vein thromboembolism	3
Other diagnosis less likely than PE	3
Tachycardia (>100 beats per minute)	1.5
Immobilization for three or more days OR surgery in the past four weeks	1.5
Previous deep vein thromboembolism or PE	1.5
Hemoptysis	1
Malignancy	1
Source: [25]	*Table 2*

TREATMENT

INITIAL MANAGEMENT

The mainstays of initial PE management focus on rapid assessment of clinical severity and stabilization of the patient. As noted, when a patient initially presents, the most critical pieces of information lie in their vital signs (e.g., heart rate, blood pressure, oxygenation). The initial goal for the patient with PE is to maintain oxygen levels. If mechanical circulatory support is required, cardiopulmonary bypass permits right ventricular recovery by decompressing the dilated and dysfunctional ventricle through diversion of the cardiac output to a pump and oxygenator [51]. Alternatively, venoarterial extracorporeal membrane oxygenation (VA-ECMO) functions similarly but is more mobile, allowing for support to be initiated and continued in more diverse settings.

For patients who are hemodynamically unstable, intravenous fluid should be given with caution, because this can lead to right ventricular overload. Hemodynamically stable, low-risk patients should receive anticoagulation alone; those who are at high risk and have hemodynamic compromise may require systemic thrombolysis or surgical- versus catheter-directed therapy. Those who are at intermediate risk have more complicated cases and can be treated with either anticoagulation alone or anticoagulation with potential procedures. As discussed,

the risk level will depend on the severity of right ventricular dysfunction on echocardiography, the degree of troponin elevation, the amount of oxygen and vasopressor required, and clot burden and location [10; 11; 12; 13]. The American Society of Hematology (ASH) recommends that patients with PE at low risk for complications be offered home treatment rather than hospital treatment [27].

The therapeutic treatment strategy for patients with a new diagnosis of PE, and venous thromboembolism in general, can be divided into three phases: initial treatment (the first three weeks after diagnosis), primary treatment (three to six months, or longer), and secondary prevention (beginning upon completion of primary therapy and continuing indefinitely) [27]. For primary treatment of patients with PE, whether unprovoked or provoked by a transient or chronic risk factor, the ASH suggests a shorter course of anticoagulation therapy (3 to 6 months) be preferred over a longer course (6 to 12 months). Anticoagulation therapy may be continued indefinitely in select patients for whom the risk for bleeding complications is less than the risk of recurrent PE.

PRIMARY PHARMACOTHERAPY

In selecting initial pharmacotherapy, European guidelines and a 2022 clinical practice review recommend that treatment be guided by risk stratification of PE as high, intermediate, or low based on the patient's clinical presentation [36; 55]. Approximately 5% of patients present with signs of high-risk PE (e.g., shock, end-organ hypoperfusion/dysfunction, blood pressure <90 mm Hg) not caused by arrhythmia, hypovolemia, or intrinsic heart failure [55]. Intermediate-risk patients are those who present with echocardiographic evidence of right heart strain, elevated cardiac biomarkers, or both; those who are hemodynamically stable with normal cardiac biomarkers and no evidence of right ventricular strain are classified as having low-risk PE. Patients classified as having high-risk PE are candidates for initial reperfusion (thrombolytic) therapy; those with intermediate- and low-risk PE should receive immediate anticoagulation therapy [36; 55]. Treatment should be started promptly whenever PE is strongly suspected and the patient's risk of serious bleeding complications is low. Pharmacotherapy options for initial anticoagulation include intravenous unfractionated heparin, subcutaneous low-molecular-weight heparin, subcutaneous fondaparinux, factor Xa inhibitors (e.g., apixaban, rivaroxaban), direct thrombin inhibitors (e.g., dabigatran), and intravenous argatroban for patients with heparin-induced thrombocytopenia.

Thrombolytic Therapy

Patients who present with high-risk PE warrant consideration for immediate reperfusion therapy, there being no contraindications (e.g., brain metastases, bleeding disorders, recent surgery) [36; 55]. Intravenous systemic thrombolysis is a readily available option for reperfusion. Thrombolytic agents act to dissolve the thrombus by converting plasminogen into plasmin. With early thrombus resolution, the elevated pulmonary arterial pressure/resistance and accompanying right ventricular dysfunction improve rapidly. Thrombus resolution within the first 24 hours in particular is much faster in thrombolytic therapy than with heparin [52].

The first recombinant tissue plasminogen activator, and the most commonly used thrombolytic agent used in patients with PE, is alteplase (rtPA); other available agents include streptokinase, urokinase, reteplase, and tenecteplase. The main indication for thrombolysis is high-risk PE with thrombus and hemodynamic instability. rtPA is administered at a rate of 50 mg per hour for two hours; the dose should be reduced for patients with weight less than 65 kg. If streptokinase, is used, a loading dose of 250,000 IU is given, followed by and infusion of 100,000 IU per hour for 24 hours. Urokinase is started with a loading dose of 4,400 IU and an infusion of 4,400 IU/kg/hour for 12 hours [29; 52].

According to the American College of Physicians, catheter-directed thrombolytic therapy can be considered if cardiopulmonary deterioration is imminent [53]. There is some evidence that ultrasound-assisted catheter-directed thrombolysis is superior to heparin anticoagulation alone in improving right ventricular dilatation within 24 hours without major bleeding complications or recurrent embolism.

ORAL ANTICOAGULATION THERAPY	
Agent	**Dosage**
Vitamin K Antagonist	
Warfarin	5 mg once daily for most patients[a]
Direct Thrombin Inhibitor	
Dabigatran etexilate	After at least 5 days of initial therapy with a parenteral anticoagulant, transition to oral 150 mg twice daily.
Factor Xa Inhibitors	
Apixaban	10 mg twice daily for 7 days, followed by 5 mg twice daily
Edoxaban	After at least 5 days of initial therapy with a parenteral anticoagulant, transition to once-daily oral 60 mg for patients >60 kg or 30 mg for patients ≤60 kg.
Rivaroxaban	15 mg twice daily with food for 21 days, followed by 20 mg once daily with food
[a]For patients who are expected to be more sensitive to warfarin, a starting dose of 2.5 mg daily is recommended. After three days of treatment, dosage should be adjusted based on INR values.	
Source: [29]	*Table 3*

Absolute contraindications to thrombolytic therapy include history of intracranial hemorrhage, known structural cerebral vascular lesion, known malignant intracranial neoplasm, recent history (within past three months) ischemic stroke, active bleeding (excluding menses), and recent history (within past three months) significant closed-head trauma or facial trauma [52; 53].

Oral Anticoagulants

Direct oral anticoagulants (DOACs) (factor Xa inhibitors or direct thrombin inhibitors) are recommended over vitamin K antagonists (e.g., warfarin) for most patients; however, those with renal insufficiency (i.e., creatinine clearance <30 mL/min), moderate-to-severe liver disease, or antiphospholipid syndrome are not good candidates for DOAC therapy [27].

EVIDENCE-BASED PRACTICE RECOMMENDATION

The European Society of Cardiology (ESC) and European Respiratory Society (ERS) recommends direct oral anticoagulants (DOACs) as first choice anticoagulants over warfarin even in those who are warfarin eligible.

(https://academic.oup.com/eurheartj/article/41/4/543/5556136. Last accessed August 18, 2023.)

Level of Evidence: Expert Opinion/Consensus Statement

Factor Xa inhibitors such as apixaban and rivaroxaban have the advantage of fixed dosing and no need for monitoring laboratory values, both of which are required of vitamin K antagonists. Rivaroxaban and apixaban do not require any kind of overlap with an intravenous agent. Dose reductions are indicated for those with renal insufficiency. Apixaban can be used in patients with renal insufficiency and is safe for patients on dialysis [2; 28]. Reversal agents are available: idarucizumab for reversal of dabigatran, and andexanet alfa for apixaban and rivaroxaban.

The half-life of factor Xa inhibitors is much shorter than the half-life of warfarin. If bleeding develops and requires reversal, a four-factor prothrombin complex concentrate can be used. Direct thrombin inhibitors such as dabigatran can also be used for treatment for these patients. For those with heparin-induced thrombocytopenia, intravenous argatroban or subcutaneous fondaparinux can be used for anticoagulation. The dosage varies according to agent (***Table 3***).

Drug-drug interactions with DOACs are common and may increase risk of bleeding or thrombosis. Important DOAC interactions are often due to medications that affect cytochrome P450 (CYP450) enzymes or transport proteins or increase bleeding propensity.

Warfarin, which used to be the mainstay of therapy, is no longer considered first choice, as the other DOACs have better safety profiles and patient satisfaction. Bleeding is common with warfarin usage and is more likely to be develop in patients who are older (65 years of age and older) and with comorbidities, such as diabetes, recent myocardial infarction, and other chronic conditions (e.g., kidney disease, stroke). If it develops, bleeding can be reversed with vitamin K at a dose of 2.5–10 mg intravenously or orally. Fresh frozen plasma can also be used with elevated prothrombin complex concentrates [5; 30; 31]. Drug interactions are also a concern with warfarin. Another potential complication is warfarin-induced necrosis, which is more likely to occur in patients with a history of heparin-induced thrombocytopenia. If warfarin is used, the dose should be adjusted to reach and maintain a target goal of an international normalized ratio (INR) of 2.5 (range: 2.0–3.0).

Heparin

Intravenous unfractionated heparin has a short half-life and can be reversed with protamine [28]. An initial bolus is given followed by an infusion, during which partial thromboplastin time (PTT) values are monitored. The dosage is based on a weight-based protocol. Although relatively safe to use, the pharmacokinetics of this drug are unpredictable, resulting in the need for close clinical monitoring. However, due to its short half-life, it can quickly be reversed, if needed.

Subcutaneous low-molecular-weight heparin has several advantages, including increased bioavailability and more predictable anticoagulation, as opposed to intravenous unfractionated heparin [28; 32]. There is also decreased incidence of bleeding and potentially better outcomes. Low-molecular-weight heparin is given at a dosage of 1 mg/kg body weight. All heparin products include similar bleeding risk profiles as well as a risk for thrombocytopenia, urticaria, and anaphylaxis. For patients with breakthrough deep vein thrombosis and/or PE during therapeutic warfarin treatment, the ASH suggests using low-molecular-weight heparin over DOAC therapy [27].

Fondaparinux

Fondaparinux is a factor Xa antagonist given subcutaneously in the management of acute PE instead of heparin. Advantages include fixed-dose administration once or twice per day, lack of need for clinical monitoring, and lower risk of thrombocytopenia. The dose is 5 mg for patients who weigh less than 50 kg, 7.5 mg for patients weighing 50–100 kg, and 10 mg for those weighing more than 100 kg. The dose should be adjusted in persons with kidney disease. It is contraindicated for patients with a creatinine clearance less than 30 mL/minute. When used for thromboprophylaxis, some experts recommend a 50% dose reduction or use of low-dose heparin instead [29].

SURGICAL MANAGEMENT

Pulmonary embolectomy is indicated for patients that have high- or intermediate-risk PE with contraindications to thrombolysis; failed thrombolysis or catheter-assisted embolectomy; or hemodynamic shock that is likely to cause death before thrombolysis can take effect [52]. Surgical pulmonary embolectomy is a procedure performed on cardiopulmonary bypass through a midline sternotomy, involving either central or femoral vessel initiation. Management involves moderate hypothermia for better visualization and protection during moments of reduced cardiopulmonary bypass flows. Aortic cross-clamping and cardioplegic arrest are sometimes unnecessary to prevent negative effects on right ventricular recovery [51]. Dual incisions offer improved visualization and better clot extraction. Various methods, such as suction, retrograde perfusion, manual manipulation, or balloon-tipped catheters, can aid clot extraction, but balloon catheters may lead to increased postprocedural complications [51].

SECONDARY PREVENTION

Maintenance anticoagulation for secondary prevention is done for patients who have extensive clot burden or to reduce the risk of new clot formation. There are multiple pharmacotherapeutic options for this phase of treatment, including factor Xa inhibitors (e.g., apixaban), dabigatran, and aspirin. Warfarin and low-molecular-weight heparin are second-line options.

Factor Xa anticoagulants, such as apixaban and rivaroxaban, are the most common first-line option for secondary prevention. Though warfarin was previously used, research has shown a decreased risk for intracranial hemorrhage with factor Xa anticoagulants compared with warfarin. When used for maintenance therapy, the dosage of apixaban is 2.5 mg twice per day; the dosage of rivaroxaban is 10 mg once per day. Cessation of therapy should be considered again after 6 to 12 months [4; 5].

Those with incidental PE, very small clot burdens, and minimal symptoms should likely be treated in an outpatient setting—unless other risk factors are present. However, patients with hemodynamically unstable PE (e.g., extensive clot burden, low blood pressure, abrupt clinical deterioration) often require an intensive care stay.

Aspirin has also been studied for long-term maintenance therapy and is more effective than placebo. However, anticoagulation is typically preferred over aspirin. When anticoagulation therapy is initiated in patients with PE with stable cardiovascular disease who were previously taking aspirin for cardiovascular risk modification, clinicians should consider suspending the aspirin during anticoagulation therapy. Enoxaparin sodium or low-molecular-weight heparin may be used in high-risk cancer patients with recurrent PE [2; 28].

Duration of Pharmacotherapy for Secondary Prevention

As noted, the duration of anticoagulation therapy for secondary prevention is dependent on a variety of factors, such as bleeding risk and risk factors for PE, and can range from three months to lifelong therapy [3; 28; 32]. If the patient experienced PE following a transient risk factor (i.e., a provoked event), such as immobilization or recent surgery or trauma, at least three months of treatment is warranted, after which therapy should be reassessed. However, those who have chronic provoked factors for PE, such as active cancer, a hypercoagulable state, or chronic immobility, may benefit from long-term (indefinite) anticoagulation therapy. When creating the treatment plan, the goal is to weigh the benefits of PE and deep vein thrombosis prevention with the risk of anticoagulation events (e.g., bleeding). Risk factors for bleeding include age 65 years or older, frequent falls, alcohol abuse, renal failure, previous stroke, diabetes, and anemia.

For patients who develop PE provoked by a transient risk factor and who have a history of a previous thrombotic event also provoked by a transient risk factor, the ASH guideline panel suggests stopping anticoagulation after completion of the primary treatment phase of therapy [27].

PE IN THE OUTPATIENT SETTING

When possible, patients at assessed low risk for complications (i.e., minimal risk of PE-related death) should be discharged from the hospital and continue to receive treatment at home. Such patients are hemodynamically stable, with have no right heart strain and normal cardiac biomarkers. Most patients with low-risk PE can be treated with an oral anticoagulant or a brief period of low-molecular-weight heparin followed by oral therapy. The presence or absence of comorbidities and proper care and anticoagulation therapy, which can be provided on an outpatient basis, should be noted. Scoring systems have been developed to stratify these patients, including the HESTIA rule (***Table 4***), the PE Severity Index (PESI), and its simplified version (sPESI) (***Table 5***) [33; 34; 35].

The PESI scales identify those with a low risk of 30-day mortality [33]. The criteria used include age, sex, history of cancer, history of chronic pulmonary disease, heart rate, systolic blood pressure, and oxygen saturation [33]. The scales relate the risk stratification score to an associated 30-day mortality and risk of death and can assist in identifying patients who may appropriately be managed at home. The patient's social situation, access to supportive care, and ability to transfer to higher level care should all be considered before shifting to outpatient management.

HESTIA EXCLUSION CRITERIA FOR OUTPATIENT TREATMENT	
Criteria	**Points[a]**
Hemodynamically unstable	1
Thrombolysis or embolectomy needed	1
Active bleeding or high risk of bleeding	1
More than 24 hours on supplemental oxygen needed to maintain oxygen saturation >90%	1
PE diagnosed during anticoagulant treatment	1
Severe pain requiring IV pain medication for more than 24 hours	1
Medical or social reason for hospital treatment for more than 24 hours (e.g., infection, malignancy, no support system)	1
Creatinine clearance of <30 mL/min	1
Severe liver impairment	1
Pregnancy	1
History of heparin-induced thrombocytopenia	1
[a]A score of 1 or more is defined as high risk and rules out outpatient treatment.	
Source: [36]	*Table 4*

THE ORIGINAL PULMONARY EMBOLISM SEVERITY INDEX (PESI) AND THE SIMPLIFIED PESI (sPESI) CLINICAL RISK SCORES		
Parameter	**PESI**	**sPESI**
Age	Age in years	1 if older than 80 years
Male sex	10	—
Cancer diagnosis	30	1
Chronic heart failure Chronic pulmonary disease	10 10	1
Pulse ≥110 beats per minute	20	1
Systolic blood pressure <100 mm Hg	30	1
Respiratory rate ≥30 breaths per minute	20	—
Temperature <36°C	20	—
Altered mental status	60	—
Arterial oxyhemoglobin saturation <90%	20	1
Risk Stratification (PESI)		
Class I (≤65 points)	Very low 30-day mortality risk (0% to 1.5%)	
Class II (66–85 points)	Low mortality risk (1.7% to 3.5%)	
Class III (86–105 points)	Moderate mortality risk (3.2% to 7.1%)	
Class IV (106–125 points)	High mortality risk (4% to 11.4%)	
Class V (>125 points)	Very high mortality risk (10% to 24.5%)	
sPESI Score		
0 points	30-day mortality risk 1%	
1 or more points	30-day mortality risk 10.9%	
Source: [37; 56; 57]		*Table 5*

Anticoagulation options to manage confirmed PE in an outpatient setting include subcutaneous low-molecular-weight heparin, fondaparinux, unfractionated heparin, or DOACs [28; 32; 38; 39]. The treatment duration is generally three to six months [38; 39]. Following the initial three-month period, the decision of whether or not to continue treatment will be made based on continued risk of recurrent thromboembolic balanced against the risks of continued anticoagulation [4; 5; 40].

PE AND COVID-19

Hospitalized patients with advanced COVID-19 may have laboratory signs of a coagulopathy and increased risk for arterial and venous thromboembolic complications, including PE [41; 42; 43]. The pathogenesis is unknown but likely involves some combination of systemic inflammation, endothelial dysfunction, platelet activation, immobility, and stasis of blood flow [43]. The earliest abnormalities are elevated D-dimer levels and mild thrombocytopenia; with disease progression, fibrin degradation products are elevated and prothrombin time becomes prolonged. Laboratory measure of coagulation factors in patients hospitalized with COVID-19 provides a way to track disease severity. The presence of an elevated D-dimer on admission carries a poor prognosis and has been associated with increased risk of requiring mechanical ventilation, intensive care unit admission, and mortality [43; 44]. The most frequently reported complications of COVID-19 coagulopathy are deep venous thrombosis and PE. In a prospective study of 150 critically ill patients from two centers in France, 25 patients developed PE and 3 developed deep vein thrombosis, despite prophylactic anticoagulation [45]. In a report of 184 patients with severe COVID-19 from three centers in the Netherlands, the cumulative incidence of venous thromboembolism was 27%, including PE in 80% of the cases affected [46]. Other centers have reported lower rates. Among 393 patients from New York, venous thromboembolism was diagnosed in only 13 patients (3.3%), 10 of whom were on mechanical ventilation [47]. The National Institutes of Health recommends all hospitalized patients with COVID-19 who experience rapid deterioration of pulmonary, cardiac, or neurological function or sudden, localized loss of peripheral perfusion be evaluated for thromboembolic disease [48].

At present, there are limited data available to inform clinical management around prophylaxis or treatment of venous thromboembolic complications in patients with COVID-19 [41]. One source of interim guidance recommends regularly monitoring hemostatic markers—namely D-dimer, prothrombin time, and platelet count—in all patients presenting with COVID-19 and prophylactic use of low-molecular-weight heparin in all hospitalized patients, unless there are contraindications [43]. The National Institutes of Health recommends that hospitalized, nonpregnant adults with COVID-19 who do not require intensive-level care and have no evidence of venous thromboembolism receive a therapeutic dose of heparin if their D-dimer levels are above the upper normal limit and they require low-flow oxygen, as long as they do not have an increased risk of bleeding [48].

Contraindications for the use of therapeutic anticoagulation in patients with COVID-19 include [48]:

- Platelet count <50 x 10^9/L
- Hemoglobin <8 g/dL
- Need for dual antiplatelet therapy
- Bleeding within the past 30 days that required an emergency department visit or hospitalization
- History of a bleeding disorder or an inherited or active acquired bleeding disorder

Low-molecular-weight heparin is preferred over unfractionated heparin because of its ease of administration and because low-molecular-weight heparin was the predominant form of heparin used in the clinical trials for COVID-19 [48].

In patients without venous thromboembolism who have started treatment with therapeutic doses of heparin, treatment should continue for 14 days or until they are transferred to intensive care or discharged from the hospital, whichever comes first. A prophylactic dose of heparin is also recommended for patients who do not meet the criteria for receiving therapeutic heparin or are not receiving a therapeutic dose of heparin for other reasons, unless a contraindication exists [48].

For those patients who develop a PE in the setting of a COVID-19 infection, about 50% will report persistent fatigue, reduced exercise tolerance, and dyspnea [14; 23]. Of these patients, one-half will also have signs of right ventricular dysfunction on echocardiogram after the diagnosis is made, referred to as post-PE syndrome. This further leads to dyspnea on exertion, damage to the venous valves in the leg, prolonged lower extremity swelling and aching, venous ulcers, and impaired quality of life.

CONCLUSION

PE is a common cause of acute-onset breathlessness and chest pain, often confused for many other diagnoses. It should remain on one's clinical differential due to the fact that it can be life-threatening and is treatable if caught and managed early. A variety of treatment options are at the forefront for ensuring that patients are given the best possible outcome.

Implicit Bias in Health Care

The role of implicit biases on healthcare outcomes has become a concern, as there is some evidence that implicit biases contribute to health disparities, professionals' attitudes toward and interactions with patients, quality of care, diagnoses, and treatment decisions. This may produce differences in help-seeking, diagnoses, and ultimately treatments and interventions. Implicit biases may also unwittingly produce professional behaviors, attitudes, and interactions that reduce patients' trust and comfort with their provider, leading to earlier termination of visits and/or reduced adherence and follow-up. Disadvantaged groups are marginalized in the healthcare system and vulnerable on multiple levels; health professionals' implicit biases can further exacerbate these existing disadvantages.

Interventions or strategies designed to reduce implicit bias may be categorized as change-based or control-based. Change-based interventions focus on reducing or changing cognitive associations underlying implicit biases. These interventions might include challenging stereotypes. Conversely, control-based interventions involve reducing the effects of the implicit bias on the individual's behaviors. These strategies include increasing awareness of biased thoughts and responses. The two types of interventions are not mutually exclusive and may be used synergistically.

Works Cited

1. Soloff LA, Rodman T. Acute pulmonary embolism. II. Clinical. *Am Heart J*. 1967;74:829.
2. Goldacre MJ, Roberts S, Yeates D, Griffith M. Hospital admission and mortality rates for venous thromboembolism in Oxford region, UK, 1975–98. *Lancet*. 2000;355:1968.
3. Smith SB, Geske JB, Kathuria P, et al. Analysis of national trends in admissions for pulmonary embolism. *Chest*. 2016;150:35.
4. Goldhaber SZ, Grodstein F, Stampfer MJ, et al. A prospective study of risk factors for pulmonary embolism in women. *JAMA*. 1997;277:642.
5. Alotaibi GS, Wu C, Senthilselvan A, McMurtry MS. Secular trends in incidence and mortality of acute venous thromboembolism: the AB-VTE population-based study. *Am J Med*. 2016;129:879
6. Goldhaber SZ, Bounameaux H. Pulmonary embolism and deep vein thrombosis. *Lancet*. 2012;379:1835-1846.
7. Bělohlávek J, Dytrych V, Linhart A. Pulmonary embolism, part I: Epidemiology, risk factors and risk stratification, pathophysiology, clinical presentation, diagnosis and nonthrombotic pulmonary embolism. *Exp Clin Cardiol*. 2013;18(2):129-138.
8. Oger E. Incidence of venous thromboembolism in a community-based study in western France. *Thromb Haemost*. 2000;83:657-660.
9. Pineda LA, Hathwar VS, Grant BJ. Clinical suspicion of fatal pulmonary embolism. *Chest*. 2001;120(3):791-795.
10. Stępniewski J, Kopeć G, Musiałek P, et al. Hemodynamic effects of ultrasound-assisted, catheter-directed, very low-dose, short-time duration thrombolysis in acute intermediate-high risk pulmonary embolism (from the EKOS-PL study). *Am J Cardiol*. 2021;141: 133-139.
11. White D, MacDonald S, Edwards T, et al. Evaluation of COVID-19 coagulopathy; laboratory characterization using thrombin generation and nonconventional haemostasis assays. *Int J Lab Hematol*. 2021;43(1):123-130.
12. Fischer JI, Huis in 't Veld MA, Orland M, Harvey P, Panebianco NL, Dean AJ. Diagnosis of near-fatal pulmonary embolus-in-transit with focused echocardiography. *J Emerg Med*. 2013;45(2):232-235.
13. Panos RJ, Barish RA, Whye DW Jr, Groleau G. The electrocardiographic manifestations of pulmonary embolism. *J Emerg Med*. 1988;6:301-307.
14. Widimský J, Malý J, Eliáš P, et al. Doporučení pro diagnostiku a léčbu akutní plicní embolie. *Vnitř Lék*. 2008;54:1S25-1S72.
15. Ryu JH, Pellikka PA, Froehling DA, Peters SG, Aughenbaugh GL. Saddle pulmonary embolism diagnosed by CT angiography: frequency, clinical features and outcome. *Respir Med*. 2007;101:1537-1542.
16. Sista AK, Kuo WT, Schiebler M, Madoff DC. Stratification, imaging, and management of acute massive and submassive pulmonary embolism. *Radiology*. 2017;284:5-24.
17. Söhne M, Ten Wolde M, Boomsma F, Reitsma JB, Douketis JD, Büller HR. Brain natriuretic peptide in hemodynamically stable acute pulmonary embolism. *J Thromb Haemost*. 2006;4:552-556.
18. El-Menyar A, Sathian B, Al-Thani H. Elevated serum cardiac troponin and mortality in acute pulmonary embolism: systematic review and meta-analysis. *Respir Med*. 2019;157:26-35.
19. Derenoncourt P-R, Felder GJ, Royal HD, et al. Ventilation-perfusion scan: a primer for practicing radiologists. *Radiographics*. 2021;41(7):2047-2070.
20. Singh M, Guha D, Patterson B. Clot in transit: point-of-care ultrasound diagnosis of acute pulmonary embolism. *J Emerg Med*. 2021;60(5):659-660.
21. Le Gal G, Righini M, Roy PM, et al. Prediction of pulmonary embolism in the emergency department: the revised Geneva score. *Ann Intern Med*. 2006;144:165-171.
22. Joseph D, Lee E, Tabatabai R, Chilstrom M. Pulmonary embolism in transit: direct visualization of a PE passing through the heart using bedside ultrasonography. *CJEM*. 2016;18(4):313-314.
23. Torbicki A, Perrier A, Konstantidines S, et al. Guidelines on the diagnosis and management of acute pulmonary embolism. *Eur Heart J*. 2008;29:2276-2315.
24. Gerges C, Skoro-Sajer N, Lang IM. Right ventricle in acute and chronic pulmonary embolism (2013 Grover Conference series). *Pulm Circ*. 2014;4(3):378-386.
25. van Belle A, Buller HR, Huisman MV, et al. Effectiveness of managing suspected pulmonary embolism using an algorithm combining clinical probability, D-dimer testing, and computed tomography. *JAMA*. 2006;295:172.
26. Kline JA, Courtney DM, Kabrhel C, et al. Prospective multicenter evaluation of the pulmonary embolism rule-out criteria. *J Thromb Haemost*. 2008;6(5):772-780.
27. Ortel TL, Neumann I, Ageno W, et al. American Society of Hematology 2020 guidelines for management of venous thromboembolism: treatment of deep vein thrombosis and pulmonary embolism. *Blood Adv*. 2020;4(19):4693-4738.
28. Stevens SM, Woller SC, Kreuziger LB, et al. Antithrombotic therapy for VTE disease: second update of the chest guideline and expert panel report. *Chest*. 2021;160:e545-608.
29. LexiComp Online. Available at https://online.lexi.com. Last accessed August 13, 2023.
30. Klarin D, Busenkell E, Judy R, et al. Genome-wide association analysis of venous thromboembolism identifies new risk loci and genetic overlap with arterial vascular disease. *Nat Genet*. 2019;51:1574.
31. Lindström S, Wang L, Smith EN, et al. Genomic and transcriptomic association studies identify 16 novel susceptibility loci for venous thromboembolism. *Blood*. 2019;134:1645.

32. Hylek EM, Regan S, Henault LE, et al. Challenges to the effective use of unfractionated heparin in the hospitalized management of acute thrombosis. *Arch Intern Med*. 2003;163:621-627.
33. Yamashita Y, Morimoto T, Amano H, et al. Validation of simplified PESI score for identification of low-risk patients with pulmonary embolism: From the COMMAND VTE Registry. *Eur Heart J Acute Cardiovasc Care*. 2020;9(4):262-270.
34. Yamashita Y, Morimoto T, Amano H, et al. Usefulness of simplified pulmonary embolism severity index score for identification of patients with low-risk pulmonary embolism and active cancer: from the COMMAND VTE Registry. *Chest*. 2020;157(3):636-644.
35. Zhou XY, Ben SQ, Chen HL, Ni SS. The prognostic value of pulmonary embolism severity index in acute pulmonary embolism: a meta-analysis. *Respir Res*. 2012;13(1):111.
36. Konstantinides SV, Meyer G, Becattini C, et al. 2019 ESC guidelines for the diagnosis and management of acute pulmonary embolism developed in collaboration with the European Respiratory Society (ERS). *Eur Heart J*. 2020;41(4):543-603.
37. Malik S, Bhardwaj A, Eisen M, Gandhi S. Advanced management options for massive and submassive pulmonary embolism. *US Cardiology Review*. 2016;10(1):30-35.
38. Baglin T, Bauer K, Douketis J, Buller H, Srivastava A, Johnson G. Duration of anticoagulant therapy after a first episode of an unprovoked pulmonary embolus or deep vein thrombosis: guidance from the SSC of the ISTH. *J Thromb Haemost*. 2012;10:698-702.
39. Cuculi F, Kobza R, Bergner M, Erne P. Usefulness of aspiration of pulmonary emboli and prolonged local thrombolysis to treat pulmonary embolism. *Am J Cardiol*. 2012;110:1841-1845.
40. Bellou E, Keramida E, Karampinis I, et al. Outpatient treatment of pulmonary embolism. *Breathe (Sheff)*. 2020;16(3):200069.
41. Centers for Disease Control and Prevention. Clinical Care Considerations. Available at https://www.cdc.gov/coronavirus/2019-ncov/hcp/clinical-care/clinical-considerations-index.html. Last accessed August 13, 2023.
42. Cannegieter S, Klok FA. COVID-19-associated coagulopathy and thromboembolic disease: commentary on an interim expert guidance. *Res Pract Thromb Haemost*. 2020;4(4):439-445.
43. COVID-19 coagulopathy: an evolving story. *Lancet*. 2020;7(6):E425.
44. Tang N, Li D, Wang X, Sun Z. Abnormal coagulation parameters are associated with poor prognosis in patients with novel coronavirus pneumonia. *J Thromb Haemost*. 2020;18(4):844-847.
45. Helms J, Tacquard C, Severac F, et al. for the CRICS TRIGGERSEP Group. High risk of thrombosis in patients in severe SARS-CoV-2 infection: a multicenter prospective cohort study. *Intensive Care Med*. 2020;46(6):1089-1098.
46. Klok FA, Kruip MJHA, van der Meer NJM, et al. Incidence of thrombotic complications in critically ill ICU patients with COVID-19. *Thrombosis Research*. 2020;191:145-147.
47. Goyal P, Choi JJ, Pinheiro LC, et al. Clinical characteristics of COVID-19 in New York City. *N Engl J Med*. 2020;382:2372-2374.
48. National Institutes of Health. COVID-19 Treatment Guidelines: Antithrombotic Therapy in Patients With COVID-19. Available at https://www.covid19treatmentguidelines.nih.gov/therapies/antithrombotic-therapy. Last accessed August 13, 2023.
49. Stowell JR, Filler L, Sabir MS, Roh AT, Akhter M. Implications of language barrier on the diagnostic yield of computed tomography in pulmonary embolism. *Am J Emerg Med*. 2018;36(4):677-679.
50. Centers for Disease Control and Prevention. Genetic Tests for Idiopathic Venous Thromboembolism: EGAPP™ Recommendation. Available at https://www.cdc.gov/genomics/gtesting/egapp/recommend/fvl.htm. Last accessed August 13, 2023.
51. Goldberg JB, Giri J, Kobayashi T, et al. Surgical management and mechanical circulatory support in high-risk pulmonary embolisms: historical context, current status, and future directions: a scientific statement from the American Heart Association. *Circulation*. 2023;147(9):e628-e647.
52. Ucar EY. Update on thrombolytic therapy in acute pulmonary thromboembolism. *Eurasian J Med*. 2019;51(2):186-190.
53. Aggarwal V, Nicolais CD, Lee A, Bashir R. Acute Management of Pulmonary Embolism. Available at https://www.acc.org/latest-in-cardiology/articles/2017/10/23/12/12/acute-management-of-pulmonary-embolism. Last accessed August 23, 2023.
54. West J, Goodacre S, Sampson F. The value of clinical features in the diagnosis of acute pulmonary embolism: systematic review and meta-analysis. *QJM*. 2007;100:763-769.
55. Kahn SR, de Wit K. Pulmonary embolism. *N Engl J Med*. 2022;387:45-57.
56. Aujesky D, Obrosky DS, Stone RA, et al. Derivation and validation of a prognostic model for pulmonary embolism. *Am J Respir Crit Care Med*. 2005;172:1041-1046.
57. Jiménez D, Aujesky D, Moores L, et al. Simplification of the pulmonary embolism severity index for prognostication in patients with acute symptomatic pulmonary embolism. *Arch Intern Med*. 2010;170:1383-1389.

Evidence-Based Practice Recommendations Citation

Konstantinides SV, Meyer G, Becattini C, et al. 2019 ESC guidelines for the diagnosis and management of acute pulmonary embolism developed in collaboration with the European Respiratory Society (ERS): The Task Force for the diagnosis and management of acute pulmonary embolism of the European Society of Cardiology (ESC). *Eur Heart J*. 2020;41(4):543-603. Available at https://academic.oup.com/eurheartj/article/41/4/543/5556136. Last accessed August 18, 2023.