



Acute

Pulmonary Embolism

**A Comprehensive Overview of
Pathophysiology, Diagnosis, Risk
Stratification, and Evidence-Based
Management**

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Acute Pulmonary Embolism: A Comprehensive Overview of Pathophysiology, Diagnosis, Risk Stratification, and Evidence-Based Management

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Abstract

Acute pulmonary embolism (PE) remains a major cardiovascular emergency and a leading cause of preventable in-hospital mortality worldwide. As the third most common acute cardiovascular syndrome after myocardial infarction and stroke, PE imposes a substantial burden on healthcare systems. This comprehensive review synthesizes current evidence on the etiology, pathophysiology, clinical presentation, diagnostic evaluation, and management of acute PE, with an emphasis on risk-stratified, guideline-directed care.

PE most commonly arises from lower-extremity deep vein thrombosis, with the classic Virchow triad of hypercoagulability, venous stasis, and endothelial injury providing a durable conceptual framework for understanding thrombotic risk. The clinical presentation is notoriously nonspecific—ranging from subtle dyspnea to sudden cardiac death—which continues to make timely diagnosis a daily challenge in emergency medicine and inpatient care. Missed or delayed diagnosis carries grave consequences: untreated PE carries a mortality of approximately 30%, whereas prompt, appropriate therapy reduces that figure to around 8%.

Modern diagnostic strategies integrate clinical probability assessment using validated tools such as the Wells criteria and Geneva score with D-dimer testing and definitive imaging, most commonly computed tomographic pulmonary angiography. Risk stratification into high-risk (hemodynamically unstable), intermediate-risk (submassive, with right ventricular dysfunction or biomarker elevation), and low-risk categories is the essential first step in management. Anticoagulation remains the cornerstone of treatment for all patients without contraindications. For high-risk PE, systemic thrombolysis or mechanical reperfusion (catheter-directed or surgical embolectomy) can be life-saving, though these interventions carry important bleeding risks that must be weighed carefully.

Long-term management requires individualized decisions regarding the duration of anticoagulation, balancing the risk of recurrent venous thromboembolism against bleeding risk. Unprovoked PE and persistent risk factors such as active cancer generally warrant extended therapy. The emergence of pulmonary embolism response teams has improved interdisciplinary coordination and outcomes. This review provides clinicians with a practical, evidence-based framework for recognizing, risk-stratifying, and managing acute PE across the spectrum of disease severity.

Keywords

Pulmonary embolism; venous thromboembolism; deep vein thrombosis; anticoagulation; thrombolysis; right ventricular failure; computed tomography pulmonary angiography; D-dimer; risk stratification; Wells criteria

Key Points

Think of PE early and often. The symptoms—dyspnea, chest pain, syncope, unexplained tachycardia—are highly

nonspecific. Maintain a low threshold for considering PE in any patient with acute-onset cardiopulmonary symptoms, especially when risk factors (immobilization, recent surgery, cancer, pregnancy, prior VTE) are present.

Use clinical prediction rules systematically. The Wells criteria and revised Geneva score are not academic exercises; they meaningfully improve diagnostic accuracy and guide the appropriate use of D-dimer and imaging. Documenting the pretest probability is a standard of care.

D-dimer is a rule-out test, not a rule-in test. A negative high-sensitivity D-dimer effectively excludes PE in low- to intermediate-probability patients. A positive D-dimer tells you only that further testing is needed—not that the patient has PE. Remember the age-adjusted D-dimer ($\text{age} \times 10 \text{ ng/mL}$ for patients over 50) to improve specificity in older adults.

Risk stratification drives treatment. The single most important initial clinical decision is distinguishing high-risk (hemodynamically unstable) PE from all others. Hypotension with systolic blood pressure $<90 \text{ mm Hg}$ for at least 15 minutes defines high-risk PE, which requires immediate consideration of thrombolysis or embolectomy. Do not wait for confirmatory imaging to escalate care in an unstable patient.

Anticoagulate early, but choose wisely. For high-probability or confirmed PE without hemodynamic instability, start anticoagulation promptly. Low-molecular-weight heparin and

fondaparinux are preferred over unfractionated heparin for stable patients. Unfractionated heparin is reserved for unstable patients who may need rapid reversal or those with severe renal impairment.

Thrombolysis saves lives in high-risk PE but carries real risks. In hemodynamically unstable patients without absolute contraindications, thrombolysis reduces mortality. In intermediate-risk (submassive) patients, the benefit is more nuanced: thrombolysis reduces the risk of decompensation but increases major bleeding, including intracranial hemorrhage. Patient selection is critical.

Duration of anticoagulation is not one-size-fits-all. All patients receive at least 3 months of anticoagulation. After that, the decision to stop or continue depends on whether the PE was provoked (by a transient risk factor) versus unprovoked, the presence of persistent risk factors (cancer, thrombophilia), and the patient's bleeding risk. Extended therapy dramatically reduces recurrence but requires shared decision-making.

Do not forget the right ventricle. Right ventricular dysfunction—assessed by echocardiography, computed tomography, or

elevated biomarkers (troponin, BNP)—identifies intermediate-risk patients who require closer monitoring. Right ventricular failure is the proximate cause of death in massive PE.

Chronic thromboembolic pulmonary hypertension is a treatable late complication. Unexplained persistent dyspnea months to years after an acute PE should prompt evaluation for CTEPH. This is not rare (up to 5% of patients) and is potentially curable with pulmonary thromboendarterectomy.

Interdisciplinary teams improve outcomes. Pulmonary embolism response teams (PERTs) bring together emergency medicine, cardiology, pulmonary/critical care, interventional radiology, and cardiac surgery to manage complex cases in real time. If your institution has a PERT, use it. If not, build informal collaborative pathways.

Introduction

Acute pulmonary embolism (PE) represents a critical, life-threatening cardiovascular emergency characterized by the partial or complete obstruction of the pulmonary arterial bed by an embolus, most frequently a thrombus

that has migrated from a distant site. By definition, PE is a form of venous thromboembolism (VTE) where the embolic material, typically originating from a deep vein thrombosis (DVT) in the lower extremities or pelvis, dislodges and traverses the right heart chambers to lodge within the pulmonary vasculature. The pathophysiological cascade is initiated when a portion of a lower-extremity DVT—often originating in the deep veins of the calf or proximal thigh—fractures and enters the systemic venous circulation. Less commonly, PE arises from non-thrombotic emboli, including air (iatrogenic or traumatic), fat (often following long bone fractures), amniotic fluid (peripartum), foreign bodies, or tumor cells, though these variants are clinically rarer and carry distinct management considerations.[1] Together, PE and DVT constitute the spectrum of VTE, a leading global contributor to morbidity, hospitalization, and mortality. The risk architecture for PE is multifactorial, encompassing both genetic predispositions—such as inherited thrombophilias (e.g., Factor V Leiden, prothrombin gene mutation)—and acquired conditions, including prolonged immobility, major surgery, active malignancy, pregnancy, and hormonal therapies.

Notwithstanding substantial advances in diagnostic imaging (e.g., computed tomography pulmonary angiography, CTPA) and therapeutic interventions (anticoagulation, thrombolysis, embolectomy), the clinical presentation of PE remains notoriously nonspecific. Cardinal symptoms—dyspnea at rest or exertion, pleuritic chest pain, syncope or presyncope, hemoptysis, and tachycardia—overlap extensively with those of other common cardiopulmonary disorders, including acute coronary syndromes, pneumonia, heart failure, and panic disorders. This symptomatic ambiguity poses a persistent diagnostic challenge for clinicians, often leading to delays in recognition and intervention. Prompt and accurate diagnosis is imperative, as untreated or delayed management of PE can precipitate rapid clinical deterioration, including progressive right ventricular (RV) dysfunction, obstructive shock, and sudden cardiac death. Clinical decision rules, such as the Wells criteria and the revised Geneva score, provide validated, standardized approaches to risk stratification and pretest probability assessment. However, suboptimal utilization of these tools in routine practice, combined with heterogeneity in therapeutic protocols across institutions, highlights an urgent need for more

consistent, evidence-based clinical pathways. Ultimately, enhanced clinician proficiency in recognizing risk factors, applying diagnostic algorithms, and initiating guideline-directed therapies is essential to improve patient outcomes and reduce the disease burden of PE.

Etiology

Risk Factors for Pulmonary Embolism

The vast majority of PEs originate as thrombi within the deep venous system of the lower extremities, particularly in the proximal veins (popliteal, femoral, iliac). Consequently, the risk factor profile for PE mirrors that of DVT, with both conditions sharing a common pathophysiological framework. The classic Virchow triad—encompassing hypercoagulability, venous stasis (or abnormal blood flow), and endothelial injury—provides a comprehensive conceptual model for understanding the predisposition to thrombus formation and subsequent embolization.

Risk factors are conventionally divided into genetic (inherited) and acquired categories. Genetic risk factors, often presenting in younger patients or those with recurrent VTE, include inherited thrombophilias such as the factor V Leiden mutation (the most common in individuals of European descent), the

prothrombin G20210A gene mutation, deficiencies of natural anticoagulants (protein C, protein S, antithrombin III), and hyperhomocysteinemia (often due to methylenetetrahydrofolate reductase (MTHFR) polymorphisms). Acquired risk factors are more prevalent in clinical practice and include prolonged immobilization (e.g., bed rest exceeding three days, long-distance travel lasting >4 hours, such as airline or car travel), recent major orthopedic surgery (especially total hip or knee arthroplasty), active malignancy (particularly adenocarcinomas of the lung, pancreas, stomach, and hematologic malignancies), indwelling central venous catheters, obesity (body mass index ≥ 30 kg/m²), pregnancy and the postpartum period, cigarette smoking, and use of oral contraceptive pills or hormone replacement therapy.[2][3][4][5] Smoking exerts a prothrombotic effect through multiple mechanisms—including increased fibrinogen levels, enhanced platelet aggregation, and endothelial dysfunction—and is an independent risk factor for all causes of pulmonary infarction, including those associated with PE.[6] Intriguingly, recent clinical studies have identified paradoxical associations regarding pulmonary infarction complicating PE: younger age (peaking around

40 years) and greater height are correlated with an increased likelihood of developing pulmonary infarction, whereas obesity appears to be associated with a reduced likelihood—a finding that may reflect differential collateral circulation or inflammatory responses.[7]

Additional predisposing factors for VTE, as cataloged in large epidemiological cohorts, include: fracture of the lower limb (especially femur or tibia); hospitalization for heart failure or atrial fibrillation/flutter within the preceding three months; hip or knee replacement surgery; major trauma (e.g., spinal cord injury, multiple fractures); a personal history of prior VTE, which confers a substantially elevated risk of recurrence; presence of central venous catheters or pacemaker leads; chemotherapy (due to both direct endothelial toxicity and procoagulant effects of certain agents); congestive heart failure or chronic respiratory failure (with associated venous stasis and inflammation); hormone replacement therapy and oral contraceptives (particularly estrogen-containing formulations); the postpartum period (due to reversal of pregnancy-associated hypercoagulable changes); systemic infections (notably pneumonia, urinary tract infection, and HIV, where inflammation and immobilization play roles); active cancer, with the highest VTE

risk observed in metastatic disease, pancreatic cancer, hematologic malignancies, lung cancer, gastric cancer, and brain cancer.[8] Infection anywhere in the body serves as a common trigger for VTE, likely mediated by acute-phase reactants, cytokine release, and transient hypercoagulability.[9] Furthermore, epidemiological evidence indicates a bidirectional relationship: patients with VTE have an increased risk of subsequent arterial thromboembolic events, including ischemic stroke and myocardial infarction, suggesting shared inflammatory and hypercoagulable pathways.[10][11]

Types of Pulmonary Embolism

A clinically meaningful classification of PE hinges upon the presence or absence of hemodynamic stability, as this stratification directly guides initial management and predicts early mortality. Hemodynamically unstable PE, historically termed “massive” or high-risk PE, is defined by sustained hypotension: systolic blood pressure <90 mm Hg for at least 15 minutes, a drop in systolic blood pressure of ≥ 40 mm Hg from baseline, or hypotension necessitating vasopressor or inotropic support in the absence of an alternative cause (e.g., sepsis, hypovolemia, arrhythmia). Critically, the outdated term “massive” does not refer to

the clot burden or size of the embolus on imaging but rather to its hemodynamic consequence—namely, obstructive shock due to acute RV failure. In such patients, mortality is driven by progressive RV dysfunction, reduced cardiac output, and impending circulatory collapse.

Conversely, hemodynamically stable PE encompasses a broad clinical spectrum, ranging from small, subsegmental, minimally symptomatic or even incidental asymptomatic PEs (low-risk or “small” PE) to larger emboli that cause mild hypotension responsive to fluid resuscitation or those that induce RV dysfunction without overt systemic hypotension. The latter category is now widely termed “submassive” or intermediate-risk PE, defined by the presence of RV dysfunction on echocardiography or elevated cardiac biomarkers (e.g., troponin, brain natriuretic peptide) in the absence of hemodynamic instability. Accurate risk stratification within this intermediate group is critical, as a subset may progress to hemodynamic compromise and benefit from more aggressive interventions.

Epidemiology

The annual incidence of acute PE in high-income countries is estimated between 39 and

115 per 100,000 population, while the incidence of DVT ranges from 53 to 162 per 100,000 individuals.[12] These figures likely underestimate the true burden, as many PE events are silent or only discovered at autopsy. Acute PE ranks as the third most common type of cardiovascular disease after coronary artery disease and stroke.[13] A notable sex difference exists, with the incidence of acute PE being higher in males than females, a disparity that may relate to differential thrombotic risk factors and hormonal influences. PE complicated by pulmonary infarction—tissue necrosis resulting from complete occlusion of a distal pulmonary artery—occurs at a rate of approximately 16% to 31% of all diagnosed PEs.[7]

Overall, PE-related mortality remains substantial. In the United States alone, PE is estimated to cause over 100,000 deaths annually, making it a leading preventable cause of in-hospital death.[14] Accurate estimation of mortality attributable to PE is methodologically challenging because many patients with sudden, unexpected cardiac death—especially those dying within one hour of symptom onset—are presumed to have sustained a massive PE, though confirmatory antemortem diagnosis is often lacking. Over recent decades, case-fatality rates for PE have decreased

significantly, a trend attributed to improved diagnostic sensitivity (widespread availability of CTPA), increased clinical awareness, earlier intervention, and the adoption of standardized risk-adjusted treatment protocols.

Pathophysiology

PE initiates a cascade of hemodynamic, gas exchange, and inflammatory derangements. When a thrombus enters the pulmonary circulation, it typically lodges at bifurcations of the pulmonary arterial tree. Multiple emboli are usually present, and the lower lung lobes are affected more frequently than the upper lobes due to greater regional blood flow; bilateral lung involvement is also common.[15] Large, central emboli may obstruct the main pulmonary artery or its primary bifurcation, creating a “saddle embolus” that, despite its dramatic appearance, can be hemodynamically well tolerated if sufficient collateral flow exists. However, saddle emboli often carry deleterious cardiovascular consequences. In contrast, smaller emboli that lodge in peripheral segmental or subsegmental arteries can lead to pulmonary infarction, characterized by intra-alveolar hemorrhage, alveolar wall necrosis, and subsequent scar formation (Hampton’s hump on imaging).

Gas Exchange Abnormalities. PE leads to impaired gas exchange through multiple mechanisms. Mechanical obstruction of the pulmonary vascular bed creates areas of high ventilation relative to perfusion—that is, increased alveolar dead space. Alveolar ventilation remains unchanged or even increased, but pulmonary capillary blood flow distal to the obstruction is reduced or absent, resulting in a mismatch of the ventilation-to-perfusion (V/Q) ratio. This dead space ventilation fails to participate in gas exchange, contributing to hypoxemia and an increased alveolar-arterial oxygen gradient. Additionally, the release of vasoactive mediators—such as serotonin (5-hydroxytryptamine), thromboxane A₂, and platelet-activating factor from activated platelets and endothelium—induces vasospasm in adjacent, initially non-occluded vessels, further decreasing pulmonary blood flow and worsening V/Q mismatch. Local accumulation of inflammatory mediators also alters pulmonary surfactant function, promoting atelectasis and stimulating respiratory drive, which manifests clinically as tachypnea and hypocapnia with respiratory alkalosis.[16]

Hemodynamic Consequences. PE substantially increases pulmonary vascular

resistance (PVR). This rise stems from two synergistic components: (1) mechanical obstruction of the vascular bed by thrombotic material, and (2) hypoxic pulmonary vasoconstriction in still-perfused but poorly oxygenated lung regions. Pulmonary artery pressure begins to rise significantly when thromboembolic occlusion involves more than 30% to 50% of the total cross-sectional area of the pulmonary arterial bed. The abrupt increase in PVR imposes a sudden afterload challenge on the thin-walled, compliant right ventricle, which is poorly adapted to acute pressure overload. The RV responds with dilation, increased wall tension, and reduced systolic function. Progressive RV dilation leads to flattening or even leftward bowing of the interventricular septum (the “D-sign” on echocardiography), which impairs left ventricular (LV) filling during early diastole. Development of a new right bundle branch block may further worsen interventricular desynchronization, reducing cardiac efficiency.

The net effect is a fall in LV preload and a consequent decline in cardiac output, leading to systemic hypotension, diminished coronary perfusion pressure, and potential myocardial ischemia. RV failure secondary to acute pressure overload is the primary cause of death

in severe PE. From a prognostic standpoint, the presence of overt clinical signs of RV failure (e.g., elevated jugular venous pressure, parasternal heave, S3 gallop) and hemodynamic instability indicates a high risk of early (in-hospital or 30-day) mortality, prompting consideration of advanced therapies such as systemic thrombolysis or embolectomy.

Pulmonary Infarction. Early literature suggested that patients with underlying cardiac or pulmonary disease—particularly those with poor collateral circulation—were at greatest risk for developing pulmonary infarction following acute PE.[18] However, recent evidence has overturned this view. Contemporary studies demonstrate that younger patients without pre-existing cardiopulmonary disease are actually more likely to suffer pulmonary infarction secondary to PE. The proposed mechanism is that chronic cardiopulmonary disease states (e.g., heart failure, chronic obstructive pulmonary disease) promote the development of robust bronchial arterial collateral circulation over time. These bronchial collaterals—derived from the systemic circulation—provide an alternative source of oxygenated blood to lung parenchyma, protecting it from ischemic necrosis despite pulmonary arterial occlusion.

In contrast, young, otherwise healthy individuals lack such collateral networks, rendering the distal lung parenchyma critically dependent on the pulmonary artery for perfusion, thus more vulnerable to infarction when a peripheral embolus occurs.[7]

The lung parenchyma receives its oxygen supply from three non-redundant sources: (1) deoxygenated blood from the pulmonary arteries (the primary source for gas exchange), (2) oxygenated blood from the bronchial circulation (systemic arteries supplying the airways and supporting structures), and (3) direct oxygen diffusion from alveolar air. Sufficient impedance of any one of these sources can theoretically cause infarction, but loss of pulmonary arterial flow is most critical. Once ischemia occurs, inflammatory mediators released from necrotic parenchyma exacerbate local vasoconstriction and bronchoconstriction, further limiting both perfusion and ventilation to the affected region.[20] If ischemia is not reversed within hours, tissue necrosis ensues, resulting in a wedge-shaped, pleura-based infarction. Unilateral infarction occurs in 77% to 87% of cases, with a strong predilection for the right lower lobe. Multiple studies consistently demonstrate a predominance of pulmonary infarction in the lower lobes relative

to the upper lobes. This is thought to reflect gravitational influences on the unique pressure relationships among alveolar, pulmonary arterial, and bronchial arterial circulations, with higher regional blood flow and perfusion pressures in the lung bases increasing both embolic delivery and the likelihood of infarction when occlusion occurs.[7][21]

History and Physical

Clinical History

A timely and accurate diagnosis of pulmonary embolism (PE) is of paramount clinical importance, given the substantial mortality and morbidity that accompany this condition—much of which is potentially preventable through early and appropriate therapeutic intervention. Landmark observational data have demonstrated that, in the absence of treatment, approximately 30% of patients with acute PE will die, whereas with prompt and effective therapy, the mortality rate falls to only 8%.[22][23] These figures underscore the critical window for diagnostic action. Paradoxically, however, establishing the diagnosis of PE remains notoriously challenging because the clinical signs and symptoms are neither sensitive nor specific. The protean manifestations of acute PE arise

from the interplay between embolic burden, underlying cardiopulmonary reserve, and individual patient factors, leading to a wide spectrum of presentations ranging from subtle, transient symptoms to fulminant hemodynamic collapse.

The most commonly encountered symptoms of acute PE include dyspnea (either at rest or with exertion), pleuritic chest pain, cough, hemoptysis, presyncope, and syncope. The character and intensity of dyspnea vary meaningfully with embolus size and location: a central, large-vessel PE often produces acute, severe, and sometimes catastrophic dyspnea, reflecting a sudden increase in right ventricular (RV) afterload and impaired gas exchange. Conversely, small peripheral emboli may cause only mild, transient dyspnea that patients might not spontaneously report, often delaying presentation. In patients with preexisting heart failure or chronic pulmonary disease—conditions that already limit cardiopulmonary reserve—a new PE may manifest solely as worsening of their baseline dyspnea, an easily overlooked “change in status” that clinicians must actively interrogate. Chest pain in PE follows two distinct pathophysiological patterns. Pleuritic chest pain, sharp and exacerbated by inspiration, typically results

from pleural irritation caused by distal emboli that induce pulmonary infarction and localized inflammation.[24] In central PE, by contrast, chest pain may arise from RV ischemia (due to increased wall tension and reduced coronary perfusion) and must be carefully distinguished from that of acute coronary syndrome or aortic dissection—conditions with overlapping presentations but radically different management.

Less common presenting features include new-onset arrhythmias (most frequently atrial fibrillation), syncope, and hemodynamic collapse.[25] Hemodynamic instability, although rare, represents a particularly critical presentation because it signifies central, extensive PE with severely compromised hemodynamic reserve—often indicating that >50% of the pulmonary arterial bed is obstructed. Syncope in the setting of PE is a high-risk feature; it is associated with a higher prevalence of hemodynamic instability and RV dysfunction, likely reflecting a transient critical reduction in cardiac output.[26] Conversely, an equally important clinical insight is that patients with even large PEs may be entirely asymptomatic or have only mild, nonspecific symptoms. Asymptomatic or incidentally discovered PE is increasingly recognized, often

found during diagnostic imaging performed for other reasons (e.g., staging computed tomography (CT) in cancer patients). Therefore, clinicians must not rely solely on symptom constellations but should actively seek risk factors for venous thromboembolism (VTE) to establish clinical pretest probability, thereby guiding the rational use of diagnostic testing.

Physical Examination Findings

The physical examination in suspected PE may be entirely normal, but when findings are present, they tend to reflect compensatory cardiorespiratory responses to increased dead space ventilation, hypoxemia, and RV pressure overload. Tachypnea (respiratory rate >20 breaths per minute) and tachycardia (heart rate >100 beats per minute) are the most common findings, yet each is highly nonspecific and may be seen in numerous other acute cardiopulmonary conditions. Examination of the lower extremities may reveal signs of deep vein thrombosis (DVT), including calf swelling, tenderness to palpation, erythema, palpable venous cords (representing thrombosed veins), or unilateral pedal edema—findings that, when present, substantially increase the pretest probability of PE. Pulmonary auscultation may demonstrate rales

(often localized) or focally decreased breath sounds, though these are neither sensitive nor specific. More specific—but less common—are physical stigmata of pulmonary hypertension and RV failure, including elevated jugular venous pressure (reflecting increased central venous pressure), a loud P2 component of the second heart sound (indicating elevated pulmonary artery pressure), a right-sided third heart sound (S3) from RV diastolic overload, and a parasternal lift or heave (suggesting RV hypertrophy or acute dilation).

PE is a well-recognized and underappreciated cause of sudden cardiac arrest, accounting for approximately 8% of such events.[27] Massive PE leading to acute RV failure presents a characteristic clinical picture: jugular venous distension, parasternal lift, RV S3, cyanosis, and hypotension (obstructive shock). A particularly important clinical scenario is the patient with known or suspected PE who presents with tachycardia and then develops sudden bradycardia or a new broad complex tachycardia, especially with a right bundle branch block (RBBB) pattern. This evolution should prompt immediate consideration of acute RV strain and impending circulatory collapse, as RBBB in this context reflects mechanical stretch or ischemia of the RV

conduction system. PE should be actively suspected in any patient presenting with hypotension accompanied by jugular venous distension after reasonable exclusion of the more common causes of this triad—acute myocardial infarction (cardiogenic shock), pericardial tamponade, and tension pneumothorax—because the management of PE in this setting differs fundamentally from these other conditions.[28]

Evaluation

Diagnostic Evaluation of Acute Pulmonary Embolus

The diagnosis of acute PE is not established by any single test in isolation but rather through an integrated, stepwise approach combining clinical probability assessment (using validated scoring systems), laboratory biomarkers, and advanced imaging. This strategy aims to minimize both missed diagnoses and unnecessary testing.

Arterial blood gas analysis. The finding of unexplained hypoxemia (low partial pressure of arterial oxygen, PaO₂) in a patient with a normal or near-normal chest radiograph (CXR) should raise immediate suspicion for PE. Common arterial blood gas (ABG) abnormalities in PE include a widened alveolar-arterial (A-a)

gradient for oxygen (indicating impaired gas exchange despite preserved alveolar ventilation), respiratory alkalosis, and hypocapnia (low partial pressure of arterial carbon dioxide, PaCO_2). These findings reflect the pathophysiological response to increased dead space ventilation: the patient hyperventilates to compensate, leading to a low PaCO_2 . Importantly, respiratory acidosis or lactic acidosis is uncommon but, when present, signals a poor prognosis—typically occurring in patients with massive PE, obstructive shock, and impending respiratory arrest.[29]

Brain natriuretic peptide. Elevations in brain natriuretic peptide (BNP) or its N-terminal prohormone (NT-proBNP) have limited diagnostic utility for the presence of PE but carry significant prognostic value.[30] Acute PE causes abrupt RV pressure overload, leading to myocardial stretch of the RV wall, which in turn releases BNP and NT-proBNP. Thus, circulating levels of these natriuretic peptides correlate with the severity of RV dysfunction in acute PE.[31] Elevated BNP or NT-proBNP in a patient with confirmed PE identifies those at higher risk of in-hospital complications and mortality.

Troponin. Serum troponin I or troponin T is a marker of myocardial injury. In the context of

PE, troponin elevation serves a prognostic rather than a diagnostic role.[32][33] The mechanism is not coronary thrombosis but rather acute RV strain with increased wall tension, reduced coronary perfusion pressure, and subendocardial ischemia—particularly of the RV. Troponin levels are elevated in 30% to 50% of patients with moderate to large PE and have been consistently linked to clinical deterioration and death after PE.[34] A normal troponin in a hemodynamically stable patient with PE suggests lower risk, whereas an elevated troponin, especially in combination with RV dysfunction on imaging, defines intermediate-risk (submassive) PE.

D-dimer. D-dimer is a fibrin degradation product generated when cross-linked fibrin is broken down by plasmin. Elevated plasma D-dimer levels indicate that the coagulation and fibrinolysis systems have been activated simultaneously—a process that occurs in acute thrombosis but also in numerous other conditions, including recent surgery, trauma, infection, inflammation, pregnancy, and malignancy. D-dimer testing has an exceptionally high negative predictive value (NPV) for VTE when a sensitive assay is used. Therefore, a normal D-dimer level makes acute PE or DVT unlikely and, in appropriate clinical

contexts, can safely exclude the diagnosis without further imaging.[35] Conversely, the positive predictive value (PPV) of an elevated D-dimer is low, so D-dimer is never used to confirm PE—only to rule it out.

Given the variety of D-dimer assays available (whole-blood agglutination, latex agglutination, enzyme-linked immunosorbent assay (ELISA)), clinicians must understand the diagnostic performance of the specific test used in their setting. Quantitative high-sensitivity ELISA methods have a diagnostic sensitivity of at least 95%. An ELISA-based D-dimer can exclude PE in patients with either low or intermediate pretest probability. The combination of a negative ELISA D-dimer with low clinical probability excludes PE in approximately 30% of suspected patients without need for further testing.

The specificity of D-dimer declines steadily with advancing age, falling to approximately 10% in patients older than 80 years. To address this limitation, age-adjusted D-dimer cut-offs have been validated for patients older than 50 years. Using an age-adjusted cut-off rather than the standard 500 ng/mL threshold increases the proportion of older patients in whom PE can be safely ruled out without increasing false-negative findings. In a pivotal study, the age-

adjusted approach raised the proportion of patients ruled out from 6.4% to 30%.[36] The recommended formula is: age (years) \times 10 ng/mL for patients older than 50. For example, a 75-year-old patient would have an age-adjusted D-dimer cut-off of 750 ng/mL (75×10). Below this threshold, PE can be excluded.

Electrocardiography. Electrocardiographic (ECG) abnormalities in suspected PE are common but notoriously nonspecific, and a normal ECG does not exclude PE.[37] The most common ECG findings include sinus tachycardia and nonspecific ST-segment or T-wave changes (particularly T-wave inversions in leads V1–V4, reflecting RV strain). The classic but uncommon S1Q3T3 pattern (an S wave in lead I, a Q wave in lead III, and a T-wave inversion in lead III), RV strain patterns, and new incomplete RBBB are seen infrequently but, when present, increase diagnostic suspicion (see Image. Electrocardiogram, Pulmonary Embolism).

Chest radiograph. In acute PE, the CXR is usually normal or shows only nonspecific abnormalities such as small pleural effusions or plate atelectasis. Its primary value lies in ruling out alternative diagnoses for dyspnea (e.g., pneumonia, pneumothorax, heart failure). However, the CXR may occasionally provide

the first clue to pulmonary infarction (see Image. Wedge-Shaped Pulmonary Infarction). Specific radiographic signs include the “Hampton hump” (a wedge-shaped, pleural-based opacity representing pulmonary infarction), the Westermark sign (regional oligemia or increased lucency due to reduced blood flow distal to an obstructed vessel), and the Fleischner sign (prominent proximal pulmonary artery). These signs are highly specific but lack sensitivity; for the Hampton hump, quoted sensitivity and specificity are 22% and 82%, respectively (see Image. Hampton Hump).[38] Other features such as atelectasis or focal consolidation are common but non-diagnostic.[39] The Westermark sign, seen in up to 2% of cases, results from a combination of proximal pulmonary artery dilation and distal vascular collapse.

Computed tomographic pulmonary angiography (CTPA). Multidetector CTPA has become the diagnostic modality of choice for suspected PE in most clinical settings. CTPA allows high-resolution visualization of the pulmonary arterial tree down to the subsegmental level.[40] The PIOPED II (Prospective Investigation On Pulmonary Embolism Diagnosis II) study reported a sensitivity of 83% and specificity of 96% for

CTPA in PE diagnosis.[41] CTPA is also the most commonly used imaging technique to diagnose pulmonary infarction when combined with appropriate clinical context (see Image. Pulmonary Embolism). CT findings associated with pulmonary infarction include a “feeding vessel sign” (a vessel leading directly to the opacity), central lucency within the opacity (representing non-enhancing necrotic tissue), and a semicircular or triangular shape. The presence of air bronchograms makes infarction less likely, as these indicate preserved airway and parenchymal architecture.[7] When a vessel sign with central lucency and no air bronchogram is present, the specificity for pulmonary infarction reaches 99%.[42]

PIOPED II further clarified the critical role of pretest clinical probability in interpreting CTPA results. A normal CTPA had a high NPV of 96% in patients with low clinical probability and 89% in those with intermediate probability. However, in patients with high pretest probability, the NPV of a normal CTPA fell to only 60%. Conversely, the PPV of a positive CTPA was high (92%–96%) in patients with intermediate or high clinical probability but only 58% in those with low pretest likelihood.[41] Thus, clinicians must actively manage discordance between clinical judgment

and CTPA findings. Current evidence supports that a negative CTPA is adequate to exclude PE in patients with low or intermediate pretest probability. Whether patients with a negative CTPA but high clinical probability require further investigation remains controversial, but many experts recommend additional testing (e.g., lower extremity compression ultrasound or V/Q scan) in this scenario.

CTPA is relatively contraindicated in moderate-to-severe iodinated contrast allergy or renal insufficiency (estimated glomerular filtration rate, eGFR <30 mL/min per 1.73 m²). The risks must be weighed against the clinical urgency of establishing a PE diagnosis. When clinically feasible, CTPA may be postponed for premedication (for allergy history) or intravenous hydration (for renal impairment). Beyond diagnosis, CTPA can detect RV enlargement, which carries prognostic value. A prospective multicenter cohort study of 457 patients found that RV enlargement (RV/left ventricular (LV) diameter ratio ≥ 0.9) was a strong, independent predictor of severe in-hospital outcomes, even in hemodynamically stable patients.[43]

Lung scintigraphy (V/Q scan). The planar ventilation-perfusion (V/Q) scan remains an established diagnostic test for suspected PE,

primarily used when CTPA is contraindicated, inconclusive, or when additional testing is needed after a non-diagnostic CTPA. A normal CXR is generally required before V/Q scanning because underlying parenchymal abnormalities increase false-positive rates. V/Q scanning is the test of choice for diagnosing PE in pregnancy (with a normal CXR) and for patients with contrast-induced anaphylaxis or severe renal failure.[44] Planar lung scan results are classically classified into three tiers: normal scan (excludes PE), high-probability scan (considered diagnostic of PE in most patients), and non-diagnostic scan (the most common category). Multiple studies have demonstrated that it is safe to withhold anticoagulation in patients with a completely normal perfusion scan.[46] An analysis from PIOPED II confirmed that a high-probability V/Q scan can confirm PE, but the PPV is insufficient to diagnose PE in a patient with low clinical probability.[47] The high frequency of non-diagnostic scans—requiring further testing—remains a major limitation.

Pulmonary angiography. Invasive pulmonary angiography, performed by injecting contrast through a right-heart catheter under fluoroscopy, was historically the gold standard for PE diagnosis. The diagnosis is made by

directly visualizing a thrombus as an arterial filling defect or the amputation of a pulmonary arterial branch.[48] With the widespread availability of CTPA, pulmonary angiography is now rarely used diagnostically, reserved for exceptional cases where a patient has high clinical probability but both CTPA and V/Q scanning are non-diagnostic. Moreover, pulmonary angiography appears inferior to CTPA in terms of inter-operator variability and diagnostic accuracy.[49] Currently, catheter-based pulmonary angiography is performed primarily when therapeutic intervention (e.g., catheter-directed thrombolysis or embolectomy) is planned, serving a combined diagnostic and therapeutic role.

Magnetic resonance angiography (MRA). MRA for suspected PE has been evaluated over several years, but large-scale studies have not supported its use as a first-line test. Limitations include low sensitivity, limited availability in emergency settings, and a high proportion of inconclusive examinations.[50] MRA may be considered only when both CTPA and V/Q scanning are infeasible. Potential advantages include no ionizing radiation exposure. In a prospective study of 371 adults with suspected PE, among the 75% with technically adequate images, MRA alone

showed a sensitivity of 78% and specificity of 99%. Among the 48% with technically adequate images for combined MRA and magnetic resonance venography, sensitivity and specificity improved to 92% and 96%, respectively.[50]

Echocardiography. Transthoracic echocardiography (TTE) can definitively diagnose PE on the rare occasion when a thrombus is directly visualized in the proximal pulmonary arteries or right heart chambers. More commonly, the diagnosis is supported by the presence of new RV strain patterns—especially in hemodynamically unstable patients. An echocardiogram showing RV dysfunction may help justify emergency thrombolytic therapy when definitive imaging cannot be obtained. However, significant limitations exist: given the complex geometry of the RV, no single echocardiographic parameter provides rapid and accurate assessment of RV size or function. Consequently, echocardiographic criteria for PE have varied across studies. Because the NPV of TTE for PE is only 40% to 50%, a negative study cannot exclude PE.[51][52] Conversely, signs of RV overload may be present without acute PE, reflecting underlying cardiac or pulmonary disease.[53]

RV dilation is seen in $\geq 25\%$ of patients with PE and is useful for risk stratification.[54] More specific findings confer high PPV for PE in patients with preexisting cardiorespiratory illness. The combination of a pulmonary ejection acceleration time < 60 milliseconds (measured in the RV outflow tract) with a peak systolic tricuspid valve gradient < 60 mm Hg (the “60/60 sign”) is suggestive of PE, as is the McConnell sign—depressed contractility of the RV free wall with relative apical sparing.[55] An RV/LV diameter ratio ≥ 1 and a tricuspid annular plane systolic excursion (TAPSE) < 16 mm are findings most frequently associated with an unfavorable prognosis.[56]

Compression ultrasonography. PE originates from lower-limb DVT in the vast majority of patients, and only rarely from upper-limb DVT (typically following venous catheterization). One study identified DVT in 70% of patients with proven PE.[57] Compression ultrasound has $> 90\%$ sensitivity and approximately 95% specificity for proximal symptomatic DVT.[58] Finding proximal DVT in a patient with suspected PE is considered sufficient to warrant anticoagulation without further diagnostic imaging for PE.[59] Because of the lower sensitivity of compression ultrasonography for distal or asymptomatic DVT, it is reserved for

patients in whom definitive imaging (CTPA or V/Q scan) is contraindicated or indeterminate.[60]

Acute Pulmonary Embolus Diagnostic Criteria

Wells criteria and Geneva score. These are the most commonly used clinical prediction rules to estimate the pretest probability of PE. They classify patients into probability categories, guiding the selection and interpretation of diagnostic tests.

Revised Geneva Clinical Prediction Rule. The original and simplified versions assign points as follows: previous PE or DVT (3/1 points); heart rate 75–94 bpm (3/1), heart rate ≥ 95 bpm (5/2); surgery or fracture within past month (2/1); hemoptysis (2/1); active cancer (2/1); unilateral lower-limb pain (3/1); pain on deep palpation and unilateral edema (4/1); age > 65 years (1/1). Using the Geneva criteria, three-level scores: low (0–3 / 0–1 points), intermediate (4–10 / 2–4), high (≥ 11 / ≥ 5). Two-level scores: PE unlikely (0–5 / 0–2), PE likely (≥ 6 / ≥ 3).

Wells Criteria (modified). Points: clinical symptoms of DVT (3 points); other diagnosis less likely than PE (3); heart rate > 100 bpm (1.5); immobilization ≥ 3 days or surgery in prior 4 weeks (1.5); prior DVT or PE (1.5);

hemoptysis (1); malignancy (1).[61]
Traditional Wells: high >6, moderate 2–6, low <2. Modified Wells: PE likely >4, PE unlikely ≤4.

Pulmonary Embolism Rule-Out Criteria (PERC). Because PE symptoms are highly nonspecific, the PERC rule was developed for emergency department patients to identify those with such low pretest probability that diagnostic workup can be withheld.[62] PERC includes eight criteria: age <50 years; heart rate <100 bpm; oxyhemoglobin saturation ≥95%; no hemoptysis; no estrogen use; no prior DVT or PE; no unilateral leg swelling; no surgery/trauma requiring hospitalization within prior 4 weeks. Patients meeting all eight criteria have a sufficiently low likelihood of PE that no further testing is indicated. PERC is valid only in clinical settings with a low prevalence of PE (<15%).[63] In settings with higher prevalence (>15%), PERC has substantially weaker predictive value.[64] Therefore, PERC should not be used in patients with intermediate or high clinical suspicion, nor in inpatients.

Diagnostic Evaluation Approach in Hemodynamically Stable Patients

An integrated approach combining clinical pretest probability, D-dimer, and definitive

imaging is standard for most hemodynamically stable patients with suspected PE.[51]

Low probability (Wells score <2). If PERC criteria are met, further testing is unnecessary, and PE is excluded. If PERC criteria are not met, obtain a D-dimer. If D-dimer is negative (<500 ng/mL, or age-adjusted cut-off in older patients), PE is excluded. If D-dimer is positive, proceed to CTPA. If CTPA is inconclusive or contraindicated, perform V/Q scan.

Intermediate probability (Wells score 2–6). Measure D-dimer. If negative, PE is excluded. If positive, perform CTPA. If CTPA inconclusive or contraindicated, perform V/Q scan.

High probability (Wells score >6). Perform CTPA emergently, provided scanner technology is adequate, the patient can lie flat and cooperate with breath-holding, body habitus permits scanning, and no iodinated contrast contraindications exist. If CTPA is inconclusive or not feasible, perform V/Q scan. A normal V/Q scan excludes PE; a high-probability V/Q scan diagnoses PE. For an intermediate-probability V/Q scan, further testing with lower extremity compression ultrasonography is appropriate.

Hemodynamically unstable patients. For patients in whom definitive imaging is unsafe, bedside echocardiography or venous compression ultrasound may be used to obtain a presumptive diagnosis of PE sufficient to justify potentially life-saving therapies (e.g., thrombolysis or embolectomy).[51]

Treatment / Management

Initial Management of Acute Pulmonary Embolus

Supportive measures. The initial approach to the patient with acute pulmonary embolism (PE) must prioritize supportive care concurrent with diagnostic and therapeutic decision-making. Supplemental oxygen should be administered to maintain oxyhemoglobin saturation at or above 90%, as hypoxemia exacerbates pulmonary vasoconstriction and impairs tissue oxygen delivery. In unstable patients, mechanical ventilation—either noninvasive (e.g., continuous positive airway pressure) or invasive via endotracheal intubation—may be required. However, clinicians must exercise caution because positive-pressure ventilation can have adverse hemodynamic consequences in the setting of acute right ventricular (RV) failure. Specifically, increased intrathoracic pressure

reduces venous return, further compromises left ventricular (LV) filling, and may precipitate circulatory collapse.

Acute RV failure is the leading cause of death in patients with hemodynamically unstable PE. A nuanced understanding of ventricular interdependence is essential for proper volume management. Aggressive volume resuscitation in such patients can over-distend the already pressure-overloaded RV, worsen interventricular septal bowing, and paradoxically reduce LV filling and cardiac output. Therefore, intravenous fluid resuscitation should be attempted only in patients with evidence of collapsible inferior vena cava (IVC) or clear intravascular depletion (e.g., from concurrent hemorrhage or dehydration). For patients who remain hypotensive despite adequate volume status, vasopressors—most commonly norepinephrine, which provides both alpha-adrenergic vasoconstriction and beta-adrenergic inotropic support—are needed to maintain systemic perfusion. In the most severe cases, mechanical cardiopulmonary support devices, such as venoarterial extracorporeal membrane oxygenation (VA-ECMO), may serve as a bridge to recovery or definitive

intervention by unloading the RV and maintaining systemic circulation.

Anticoagulation. It is vital to recognize that anticoagulation constitutes the cornerstone of treatment for acute PE, addressing both the existing thrombus and the prevention of further thromboembolic events. Three classes of parenteral anticoagulants are available for initial management: low-molecular-weight heparin (LMWH), fondaparinux (a synthetic factor Xa inhibitor), and unfractionated heparin (UFH). LMWH and fondaparinux are preferred over UFH in most hemodynamically stable patients because they are associated with a lower incidence of major bleeding and heparin-induced thrombocytopenia (HIT), have more predictable pharmacokinetics, and do not require routine monitoring of activated partial thromboplastin time.[65][66] UFH is generally reserved for specific situations: patients with hemodynamic instability in whom primary reperfusion treatment (thrombolysis or embolectomy) might be required, patients with severe renal impairment (creatinine clearance <30 mL/min, where LMWH accumulates), and those at very high bleeding risk where the short half-life of UFH offers a reversible advantage. Once the patient is stabilized, transition to long-term oral anticoagulation with newer oral

anticoagulants (NOACs) or vitamin K antagonists (VKAs) is standard practice. (Level of evidence: A1)

Anticoagulation and hemodynamic stability. The treatment strategy for patients with suspected PE is stratified according to both the presence or absence of hemodynamic instability and the clinician's index of suspicion as quantified by validated clinical prediction rules (revised Geneva or Wells score), which classify patients into low, intermediate, or high clinical probability categories.

For hemodynamically stable patients with high clinical suspicion of PE, anticoagulation should be initiated before diagnostic imaging is obtained, as the pretest probability is sufficiently high that the benefits of early treatment outweigh the risks of unnecessary anticoagulation in the small proportion who will ultimately have an alternative diagnosis. For hemodynamically stable patients with low clinical suspicion, if diagnostic imaging can be performed within 24 hours, it is appropriate to wait for imaging studies to establish a definitive diagnosis before starting anticoagulation, thereby avoiding unnecessary treatment in the majority who will not have PE. For hemodynamically stable patients with intermediate clinical suspicion, a more time-

sensitive approach is warranted: if diagnostic imaging can be performed within 4 hours, clinicians should wait for imaging results. When anticoagulation is contraindicated in a patient with confirmed PE—for example, due to active major bleeding, recent intracranial or spinal surgery, or severe thrombocytopenia—IVC filter placement should be considered as a mechanical alternative to prevent further emboli from reaching the pulmonary circulation.

For patients with high clinical suspicion who are hemodynamically unstable, emergent diagnostic imaging is indicated whenever possible. The modality of choice depends on local resources and patient stability: CTPA if the patient can be safely transported and imaged, portable perfusion scanning if available, or bedside transthoracic echocardiography (which can demonstrate RV strain or directly visualize thrombus). Primary reperfusion treatment—most commonly systemic thrombolysis—is the treatment of choice for hemodynamically unstable (high-risk, formerly "massive") acute PE, as it restores pulmonary blood flow, reduces RV afterload, and can be life-saving. Alternative reperfusion options include surgical pulmonary embolectomy or percutaneous catheter-directed

therapy, particularly in patients with absolute contraindications to thrombolysis or those who have failed thrombolytic therapy. Following successful reperfusion and hemodynamic stabilization, patients recovering from high-risk PE can be transitioned from parenteral to oral anticoagulation.

Reperfusion Strategies

Thrombolysis. Thrombolytic therapy has demonstrated effective reduction in pulmonary artery pressure and pulmonary vascular resistance in patients with PE compared with UFH alone; these improvements are assessed by echocardiography as decreased RV dilation and improved RV function.[67][68] Thrombolysis is preferred when therapy can be instituted within 48 hours of symptom onset, as early administration achieves the greatest thrombus resolution. However, clinical benefit has still been observed in patients whose symptoms began less than 14 days previously, suggesting that some degree of reversibility persists.[69] A meta-analysis of randomized controlled trials indicated a significant reduction in all-cause mortality and recurrent PE with the use of thrombolytics, albeit with an increased risk of major bleeding, including intracranial hemorrhage.[70] (Level of evidence: A1)

The landmark Pulmonary Embolism Thrombolysis (PEITHO) trial specifically examined the role of thrombolysis in hemodynamically stable patients with intermediate-risk (submassive) PE—those with RV dysfunction on imaging or elevated cardiac biomarkers but without systemic hypotension.[71] PEITHO demonstrated that thrombolysis (with tenecteplase) was associated with a significant reduction in the primary endpoint of hemodynamic decompensation or collapse. However, this benefit came at the cost of a substantially increased risk of major bleeding, including a 2% incidence of hemorrhagic stroke.[71][72] These findings have led to a nuanced recommendation: thrombolysis is not routinely recommended for all intermediate-risk PE patients but may be considered in selected patients with evidence of severe RV dysfunction, high-risk features (e.g., large thrombus burden, persistent tachycardia, declining systolic blood pressure not yet meeting criteria for hypotension), and a low bleeding risk.

Absolute contraindications to thrombolysis include: any prior intracranial hemorrhage; known structural intracranial cerebrovascular disease (e.g., arteriovenous malformation,

aneurysm); known malignant intracranial neoplasm; ischemic stroke within the past 3 months; suspected aortic dissection; active bleeding or bleeding diathesis; recent surgery encroaching on the spinal canal or brain; and recent significant closed-head or facial trauma with radiographic evidence of bony fracture or brain injury. Relative contraindications (requiring careful risk-benefit assessment) include transient ischemic attack within 6 months, uncontrolled hypertension (systolic >180 mm Hg or diastolic >110 mm Hg), dementia, pregnancy, recent major surgery (within 3 weeks), and recent cardiopulmonary resuscitation.

Catheter-directed treatment. Catheter-directed treatment encompasses a variety of percutaneous techniques, including ultrasound-assisted thrombolysis (which uses low-frequency ultrasound to enhance fibrin penetration), suction embolectomy, rotational embolectomy, thrombus aspiration, and combined mechanical fragmentation with pharmacological catheter-directed thrombolysis. These approaches are typically reserved for patients with high-risk or selected intermediate-risk PE who have contraindications to systemic thrombolysis or in whom systemic thrombolysis has failed.

Different studies have reported success rates—defined as hemodynamic improvement, reduction in RV/LV ratio, or survival—of up to 87% for catheter-directed therapies.[73][74] However, catheter-assisted embolectomy techniques carry inherent risks, including perforation of the pulmonary arteries leading to massive hemoptysis or cardiac tamponade. These complications are rare but often fatal, underscoring the need for operator expertise and appropriate patient selection. (Level of evidence: A1)

Surgical embolectomy. Surgical pulmonary embolectomy is generally indicated for patients with hemodynamically unstable (high-risk) PE in whom systemic or catheter-directed thrombolysis is absolutely contraindicated or has failed.[75][76][77] Surgical embolectomy involves cardiopulmonary bypass with median sternotomy, direct incision of the main pulmonary artery, and manual extraction of thrombus. Comparative studies have shown no difference in mortality between thrombolysis and surgical embolectomy, but the thrombolysis group had a higher risk of stroke and repeated interventions, whereas surgery carries risks of anesthesia, bleeding, and postoperative complications.

Vena cava filters. IVC filters are mechanical devices placed percutaneously into the inferior vena cava to trap emboli originating from lower-extremity deep veins, preventing their passage into the pulmonary circulation. Filters are indicated in patients with VTE who have an absolute contraindication to anticoagulation (e.g., active intracranial hemorrhage, recent major surgery) and in patients with recurrent VTE despite adequate therapeutic anticoagulation (so-called "anticoagulation failure"). Retrievable filters are strongly preferred over permanent filters. The rationale is that once the contraindication to anticoagulation has resolved (e.g., bleeding risk diminishes, surgery heals), the filter should be removed, and the patient transitioned to anticoagulation. This practice is supported by the Prevention of Recurrent Pulmonary Embolism by Vena Cava Interruption (PREPIC) study, which showed that insertion of a permanent IVC filter was associated with a significant reduction in the risk of recurrent PE but, paradoxically, a substantial increase in the risk of DVT over the long term, without a significant difference in the risk of recurrent VTE or death.[78] (Level of evidence: A1)

Long-Term Treatment and Prevention of Recurrence

The aims of anticoagulation after the acute management of PE are twofold: first, to complete treatment of the acute thrombotic episode, allowing endogenous fibrinolysis to restore vessel patency; and second, to prevent the recurrence of VTE over the long term. Clinical trials have systematically assessed various durations of anticoagulant therapy with VKAs for VTE.[79][80][81] The findings from these studies have established a consensus treatment protocol for acute PE. (Level of evidence: A1)

First, all patients with confirmed PE should receive at least 3 months of anticoagulant treatment. This initial period is necessary to prevent early recurrence and extension of thrombus. Second, after the initial 3 to 6 months, the risk of recurrence is expected to be similar whether anticoagulants are stopped at 3 to 6 months compared with more prolonged treatment periods (e.g., 12 to 24 months). That is, extending treatment beyond 3 to 6 months does not further reduce the risk of recurrence once anticoagulation is ultimately stopped. Third, extended oral anticoagulant treatment (beyond 6 months) reduces the risk of recurrent VTE by up to 90% *while the patient is on treatment*. However, this benefit is partially offset by the risk of major bleeding, which

occurs at an annual rate of approximately 1–3% with VKAs and somewhat lower with NOACs. Critically, oral anticoagulants do not eliminate the underlying predisposition to VTE; after discontinuation, the risk of recurrence returns to baseline.[79] (Level of evidence: A1)

Approximately 30% of PEs are classified as unprovoked (or idiopathic), meaning they occur in the absence of any identifiable transient or persistent risk factor. Unprovoked PE is associated with a 2- to 3-fold increase in the risk of recurrence compared to patients who had a provoked PE (e.g., following surgery, trauma, or prolonged immobility).[82] Patients with persistent risk factors—most notably active cancer, antiphospholipid antibody syndrome, or inherited thrombophilias with a strong phenotype—have a higher rate of recurrence than those with transient risk factors.[83] (Level of evidence: A1)

Consequently, the optimal duration of anticoagulation remains a matter of clinical judgment and should be individualized based on the patient's risk-benefit profile. A minimum of 3 months is recommended for all patients. Extended therapy (beyond 3 months) is indicated if the PE was unprovoked or if persistent risk factors are evident.[82] The need for longer anticoagulation should be reassessed

at the end of 3 months by formally evaluating the patient's bleeding risk using validated tools (e.g., HAS-BLED score). Those with a high bleeding risk—such as older adults with renal impairment, prior gastrointestinal bleeding, or poorly controlled hypertension—may appropriately limit therapy to 3 months. Special considerations are required for patients with active cancer, given their substantially increased risk of recurrent VTE (annual recurrence rates of 10–20% without anticoagulation). Hence, cancer patients should receive extended-duration anticoagulation as long as their bleeding risk remains acceptable (low or moderate). For cancer-associated thrombosis, LMWH and direct oral anticoagulants (specifically apixaban, rivaroxaban, and edoxaban) are preferred over VKAs based on randomized trial evidence showing lower recurrence rates or similar efficacy with reduced bleeding.[84] (Level of evidence: A1)

Differential Diagnosis

Because PE presents with an extraordinarily heterogeneous clinical picture—ranging from mild, transient dyspnea to sudden cardiac arrest—the differential diagnosis is correspondingly broad.[85] Key diagnostic considerations include:

- **Acute coronary syndrome** (ST-elevation and non-ST-elevation myocardial infarction): Chest pain, dyspnea, and syncope overlap; troponin may be elevated in both; ECG findings differentiate but are not absolute.
- **Stable angina** (chronic exertional chest pain)
- **Acute pericarditis**: Sharp, positional chest pain with pericardial friction rub and diffuse ST elevations
- **Congestive heart failure** (acute decompensated): Dyspnea, elevated jugular venous pressure, peripheral edema; BNP is elevated in both but usually more markedly in heart failure
- **Malignancy** (primary lung or metastatic): May mimic PE symptoms and coexist as a risk factor
- **Cardiac arrhythmias** (especially atrial fibrillation, supraventricular tachycardia): Palpitations, dyspnea, syncope
- **Pneumonia**: Fever, productive cough, focal rales, infiltrates on CXR; D-dimer may be elevated
- **Pneumonitis** (aspiration or chemical)

- **Pneumothorax:** Sudden pleuritic chest pain, decreased breath sounds, hyperresonance; CXR shows visceral pleural line
- **Vasovagal syncope:** Provoked by pain, fear, or dehydration; no hemodynamic instability or hypoxia

Prognosis

The presence of shock (persistent hypotension) and RV dysfunction confers a poor prognosis and independently predicts mortality in patients diagnosed with PE.[63] Patients with PE and a coexisting DVT are also at increased risk for death, likely reflecting a larger overall thrombus burden and higher likelihood of recurrent embolism. While earlier historical reports described a high mortality rate following pulmonary infarction (due to infection, pleural complications, or persistent respiratory failure), a 2018 study found that the survival-to-discharge rate for patients with pulmonary infarction complicating PE was high—approximately 97%.[86]

Several prognostic models have been developed to risk-stratify patients with PE, but the Pulmonary Embolism Severity Index (PESI) and its simplified version (sPESI) are the most extensively validated and commonly

used in clinical practice. The PESI score predicts 30-day mortality in patients with an established diagnosis of PE.[87] Its principal clinical utility lies in identifying patients at low risk for 30-day mortality (PESI classes I and II, or sPESI score of 0), who may be candidates for early discharge or outpatient management.

Original and Simplified Pulmonary Embolism Severity Index. The following parameters are utilized in each version (original PESI [87] / simplified sPESI [88]): age >80 years (0 / 1 point in sPESI, though original PESI uses continuous age scoring); male sex (+10 points / not included); cancer (+30 points / 1 point); chronic heart failure (+10 points / 1 point); chronic pulmonary disease (+10 points / 1 point); pulse rate ≥ 110 beats per minute (+20 points / 1 point); systolic blood pressure <100 mm Hg (+30 points / 1 point); respiratory rate >30 breaths per minute (+20 points / not included in sPESI); temperature <36 °C (+20 points / not included); altered mental status (+60 points / not included); arterial oxyhemoglobin saturation <90% (+20 points / 1 point).

Risk stratification in original PESI yields the following classes: Class I (≤ 65 points): low 30-day mortality risk, 1.0–1.6%; Class II (66–85 points): low mortality risk, 1.7–3.5%; Class III

(86–105 points): moderate mortality risk, 3.2–7.1%; Class IV (106–125 points): high mortality risk, 4.0–11.4%; Class V (>125 points): high mortality risk, 10.0–24.5%.

Risk stratification in sPESI is binary: 0 points confers a 1.0% 30-day mortality risk; ≥ 1 point confers a 10.9% 30-day mortality risk, justifying hospitalization and closer monitoring.

Complications

The primary complications associated with PE include recurrent thromboembolism, chronic thromboembolic pulmonary hypertension (CTEPH), RV failure, cardiogenic shock, and, if untreated, death. Untreated PE carries a mortality of up to 30%. Studies have also suggested an increased risk of ischemic stroke in patients with acute PE, thought to be due to paradoxical embolism via a patent foramen ovale—a common anatomical variant present in approximately 25% of the population—through which a venous thrombus can cross to the systemic arterial circulation.[89]

Recurrent Thromboembolism. In the first 1 to 2 weeks following diagnosis, patients may clinically deteriorate due to recurrent embolic events. Inadequate anticoagulation—whether due to subtherapeutic dosing, non-adherence, or

drug interactions—is the most common reason for recurrent VTE while on therapy. Therapeutic drug monitoring (for VKAs) or assessment of renal function (for LMWH and NOACs) is essential to prevent this complication.

Chronic Thromboembolic Pulmonary Hypertension.

The development of persistent or progressive dyspnea, particularly during the first 3 months to 2 years after diagnosis, should prompt the clinician to investigate CTEPH, which affects up to 5% of patients following acute PE. In patients who remain persistently symptomatic months to years after an acute PE, follow-up CT, V/Q scan, or echocardiography should be performed. On V/Q scan, patients with CTEPH typically have at least one segmental or larger mismatched perfusion defect (normal ventilation, absent perfusion). For patients with evidence of CTEPH on V/Q scanning, right heart catheterization and pulmonary angiography are indicated to confirm pulmonary hypertension (mean pulmonary artery pressure ≥ 25 mm Hg at rest), quantify its severity, exclude competing diagnoses (e.g., pulmonary arterial hypertension, left heart disease), define the surgical accessibility of obstructing thrombotic lesions (proximal vs. distal), and confirm that

an acceptable component of elevated pulmonary vascular resistance is due to surgically accessible disease rather than distal arteriopathy. For all patients with CTEPH, lifelong anticoagulant therapy is recommended to prevent recurrent thromboembolism. Early referral for evaluation for pulmonary thromboendarterectomy (PTE)—a potentially curative surgical procedure—is highly recommended, as PTE can significantly reduce pulmonary artery pressures and improve functional outcomes.

Postoperative and Rehabilitation Care

Individuals who survive acute PE often demonstrate multiple functional deficits, including reduced respiratory volume (decreased forced vital capacity and diffusing capacity), diminished exercise tolerance (decreased peak oxygen consumption on cardiopulmonary exercise testing), and significantly impaired reported quality of life. Approximately half of survivors experience persistent symptoms—most commonly dyspnea on exertion and fatigue—that reduce their physical capacity and limit return to previous activities of daily living or employment. Ongoing research is needed to identify risk factors that predict which individuals are more likely to experience

significant long-term deficits following PE resolution, as these patients may benefit most from structured rehabilitation.

The results of various studies have demonstrated heterogeneous rehabilitation protocols following PE, with program initiation times ranging from several weeks to several months after diagnosis. These studies consistently demonstrate minimal risks (low rates of bleeding or recurrent VTE) and favorable outcomes, including significant reduction in dyspnea (as measured by the Borg scale or Medical Research Council dyspnea score) and improvement in exercise capacity (6-minute walk test distance), functional mobility, and quality of life (SF-36 or EQ-5D instruments).[90][91] Rehabilitation services should work closely with the multidisciplinary care team—including pulmonologists, cardiologists, and physical therapists—to identify deficits through formal functional assessments and develop a tailored, progressive care plan that addresses these deficits within safe parameters for each patient.

Pearls and Other Issues

A timely diagnosis of PE is crucial because of the high associated mortality and morbidity, which are largely preventable with early,

appropriate treatment. Patients should be educated about the signs and symptoms of VTE (unilateral leg swelling, pain, warmth) and PE (sudden dyspnea, chest pain, hemoptysis, syncope) because the incidence of recurrent thromboembolism remains substantial even after a first event. Notably, 30% of untreated patients with PEs die, whereas only 8% die after timely therapy—a stark reminder of the life-saving potential of prompt recognition and intervention.

Team Outcomes

Effective management of acute PE requires seamless interprofessional collaboration to enhance patient-centered care, improve outcomes, and ensure patient safety. Pulmonary Embolism Response Teams (PERTs) have emerged as an innovative, structured approach to addressing the complexities and time-sensitivity of PE treatment. Composed of specialists in pulmonary medicine, critical care, cardiology, interventional radiology, and cardiothoracic surgery, PERTs facilitate prompt diagnosis, risk stratification, and timely intervention, ensuring that patients benefit from the collective expertise of diverse disciplines in real time. Studies demonstrate that PERTs improve communication, streamline treatment pathways (reducing time to therapeutic

decision), and lead to more coordinated and effective care, particularly for high-risk and intermediate-risk patients where treatment choices—anticoagulation alone, thrombolysis, catheter-directed therapy, or surgical embolectomy—have major implications for outcomes.

In the larger framework of an interprofessional healthcare team, nurses, pharmacists, and advanced practitioners play pivotal roles alongside physicians. As frontline clinicians, nurses contribute critical observations—monitoring for signs of hemodynamic deterioration, bleeding complications, or inadequate oxygenation—and ensure the timely implementation of prophylactic (e.g., early ambulation, sequential compression devices) and therapeutic interventions. Pharmacists, as experts in anticoagulation therapy, provide essential input on drug selection, dosing in renal or hepatic impairment, monitoring parameters (e.g., anti-factor Xa levels for LMWH), contraindications, and potential drug-drug interactions (particularly with VKAs and NOACs), thereby ensuring both safety and efficacy of treatment. Open communication, shared mental models, and mutual respect among all healthcare professionals allow for comprehensive and well-informed decision-

making, empowering each team member to contribute actively to patient care.

By fostering a collaborative environment, PERTs and interprofessional teams optimize care coordination and team performance. This approach emphasizes shared responsibilities, effective communication, and a unified strategy, leading to enhanced patient outcomes and improved safety in managing acute PE. Integrating diverse expertise within a cohesive team ensures that patients receive timely, evidence-based, patient-centered care across the entire care continuum—from emergency department presentation to hospital discharge and long-term follow-up.

Conclusion

Acute pulmonary embolism occupies a challenging intersection of common presentation, protean manifestations, and high stakes. Over the past two decades, we have witnessed remarkable progress—from highly sensitive D-dimer assays and multidetector computed tomography to direct oral anticoagulants and catheter-based reperfusion therapies. Yet the fundamental clinical challenge remains unchanged: the need to suspect PE in a timely manner, to risk-stratify patients accurately, and to match treatment

intensity to the true threat posed by the embolus.

No single diagnostic test or therapeutic algorithm replaces thoughtful clinical judgment. The Wells criteria and Geneva score are tools, not substitutes, for careful history-taking and physical examination. A negative D-dimer is reassuring only when the pretest probability is appropriately low. A positive computed tomography pulmonary angiogram must be interpreted in the context of the clinical picture. Anticoagulation, the mainstay of therapy, requires ongoing reassessment of risks and benefits, particularly as patients transition from acute hospitalization to long-term management.

Perhaps the most important lesson from decades of clinical research is that PE is not a monolithic disease. A small, distal, incidental PE in a young patient with a transient risk factor is a fundamentally different condition from a massive, central PE causing obstructive shock in an elderly patient with cancer. Treatment must be tailored accordingly. Over-treatment exposes patients to unnecessary bleeding; under-treatment leaves them vulnerable to recurrence and death.

Looking forward, the continued refinement of pulmonary embolism response teams, the development of more selective thrombolytic strategies, and the integration of patient-reported outcomes into long-term care decisions will further improve outcomes. For the practicing clinician, the core message is straightforward and timeless: maintain a high index of suspicion, risk-stratify early, anticoagulate wisely, and never stop learning from the patients you care for. In doing so, we can continue to reduce the mortality and morbidity of a condition that remains, all too often, a silent and preventable killer.

Declaration:

LLM utilized for minimal-edit grammatical error correction.

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