7 Pulmonary Embolism and Massive DVT for Emergency Critical Care

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Introduction

Venous thromboembolism (VTE) as a first event occurs in 100 per 100,000 persons each year in the United States with an incidence that rises exponentially with age [1]. More than 60% of symptomatic VTE cases manifest as deep vein thrombosis (DVT) alone, whereas one-third of patients present with pulmonary embolism (PE) [1]. Recurrence occurs in approximately 7% of patients and happens more frequently with PE than DVT [1, 2]. The incidence of death within 30 days of diagnosis occurs in 6% of patients with DVT and 12% with PE [1]. Less common manifestations of venous thrombosis include phlegmasia alba dolens, phlegmasia cerulea dolens (PCD), and venous gangrene, which form a clinical spectrum that carries significant morbidity [3, 4]. It is important for the emergency practitioner (EP) to appropriately recognize and treat VTE, as delays in diagnosis and treatment may result in a significant increase in morbidity and mortality.

Phlegmasia Alba Dolens, Phlegmasia Cerulea Dolens, and Venous Gangrene

Phlegmasia has been described in the medical literature as far back as the sixteenth century, though much of the formative work describing the pathophysiology was completed over the last 200 years [5–8]. All three manifestations result from acute massive venous thrombosis and obstruction of the venous drainage of an extremity. Phlegmasia alba dolens, PCD, and venous gangrene are more common during the fifth and sixth decades of life, but can occur at any age [3, 8–10]. The incidence of all three entities is higher in females than in males. Malignancy is the most commonly associated trigger and is present in approximately 20–40% of patients with PCD [3, 11].

Other associated risk factors include thrombophilia, trauma, surgery, heparin-induced thrombocytopenia, inflammatory bowel diseases, heart failure, vena cava filter insertion, and pregnancy [9, 11, 12]. Finally, 10% of patients with phlegmasia have no apparent risk factors identifiable [10]. PCD of the upper extremities is rare (<5% of patients), while PCD of the lower extremities is more common with the left-sided occurrence being three to four times more common than the right-sided occurrence [4, 12].

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Pathophysiology

Phlegmasia is caused by massive thrombosis and occlusion of the major venous channels (commonly iliofemoral veins), causing significant compromise to venous outflow and venous hypertension [12]. In phlegmasia alba dolens, the thrombosis involves only major deep venous channels of the extremity and spares the collateral veins. The venous drainage, though decreased, is still present, which reduces venous congestion and the resultant tissue ischemia which differentiates this entity from PCD. In PCD, the thrombosis extends to collateral veins causing near complete occlusion of outflow, resulting in venous congestion with massive fluid sequestration, significant edema, and tissue ischemia with bluish discoloration [3, 12, 13]. Early phases of phlegmasia are reversible if proper measures are taken to prevent venous gangrene. Capillary involvement occurs in 40–60% of PCD cases which results in irreversible venous gangrene that extends to the skin, subcutaneous tissue, or muscle [12–15]. Under this extreme, the hydrostatic pressure in arterial and venous capillaries exceeds oncotic pressure, causing fluid sequestration in the interstitium and increased compartment pressures [16, 17]. Venous pressure may increase rapidly, and fluid sequestration may reach 6–10 L [11, 18]. Circulatory shock and arterial insufficiency may ensue. Though the exact mechanism for the arterial compromise is not completely clear, it is believed to be associated with the dysregulation of coagulation and fibrinolysis and circulatory collapse from the loss of venous return [9, 12].

Key Points

- Phlegmasia occurs more commonly with advancing age (greatest in the fifth and sixth decades of life) and is more common in females.
- All three clinical entities more commonly occur in the lower extremity.
- Of the causative factors associated with VTE, cancer is most commonly associated with phlegmasia.
- The pathophysiology of phlegmasia is caused by massive thrombosis and occlusion of the major venous channels (commonly iliofemoral veins) causing significant compromise to venous outflow and venous hypertension which can eventually encroach on tissue perfusion causing tissue gangrene.

Patient Presentation

Manifestations of phlegmasia may be insidious or fulminant. Of PCD cases, 50–60% are preceded by phlegmasia alba dolens, with symptoms of edema, pain, and blanching (alba) without cyanosis [12]. The blanching, which previously was thought to be caused by arterial vasospasm, is caused by subcutaneous edema, without overwhelming venous congestion and ischemia, leaving the leg swollen and white appearing giving rise to the term "milk leg" [12].

Patients with PCD present with the clinical triad of severe edema, agonizing pain, and cyanosis [12]. Massive fluid sequestration may lead to bleb and bullae formation. Though the pathognomonic cyanosis (cerulea) in PCD usually starts distally and extends proximally, the constant pain usually starts at the femoral triangle and progresses to the entire extremity [12]. When venous gangrene occurs, it usually follows a similar distribution to the cyanosis [4, 19]. Arterial pulses may be present if venous compromise is superficial; however, when gangrene involves the muscular compartment, the resultant increased compartment pressures may produce a pulse deficit [9]. Arterial signals may be intact though difficult to appreciate because of the significant edema [12]. Patients with fulminant disease usually present with sudden severe pain, swelling, cyanosis, venous gangrene, and compartment syndrome that together impair venous outflow

and arterial supply, such that circulatory collapse and shock frequently ensue [9].

Diagnostics

The diagnoses of phlegmasia alba dolens, phlegmasia cerulea dolens (PCD), and venous gangrene can be made mainly by clinical presentation with the assistance of additional imaging for confirmation. Although contrast venography was once considered the standard for diagnosis, technical difficulties can be common (in as many as 20–25% of patients) [9, 15]. Venography, an invasive test, relies on timely support from our radiology or vascular surgery colleagues. Ascending venography can be challenging as the presence of extensive deep system thrombosis can result in nonvisualization of the deep system and a nondiagnostic study result [12, 15]. Continued improvements in ultrasonography have made this modality a faster, less expensive, and noninvasive way to assess the venous system. It has in many ways become a more reliable and accurate way to assess for proximal deep venous thrombosis (DVT) with less morbidity and can be repeated as needed to monitor for thrombus propagation or vessel recanalization (Fig. 7.1). Computer tomographic angiography (CTA) and venography may be used to evaluate clot burden, and if time allows, magnetic resonance venography can provide additional diagnostic data about vessel integrity and tissue compromise.

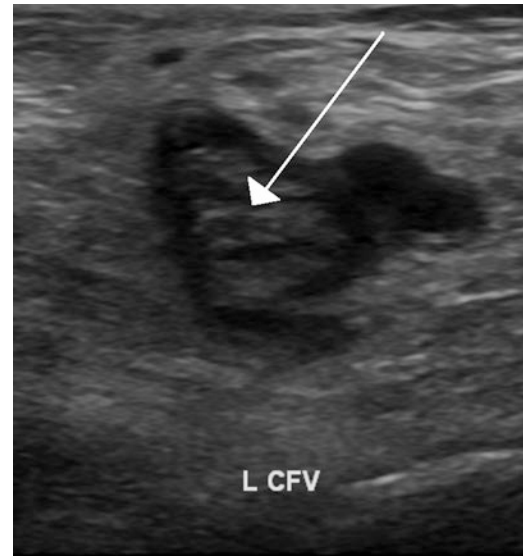

Fig. 7.1 Duplex ultrasound showing clot propagation into the common femoral vein (CMV)

Medical Therapy

The standard treatment of phlegmasia and venous gangrene is still evolving as the disease presentation is rare. The optimal therapeutic modality remains under debate and most data on therapeutic trends have been generated by case series and expert consensus [20]. So far, the results of treatment for early forms of phlegmasia have been moderately successful. Therapeutic intervention is typically multimodal, and successful intervention relies on expert consultation from interventional radiology, vascular surgery, surgery, and/or medicine depending on expert availability and institutional procedures. Therapy is aimed at preventing progression to venous gangrene by reducing venous hypertension and high interstitial pressures through restoring venous outflow to the affected extremity [12]. Conservative medical treatments, such as steep limb elevation, anticoagulation with intravenous administration of heparin, and fluid resuscitation, should be the initial course of therapy for phlegmasia alba dolens and mild nongangrenous forms of PCD [12, 20]. More invasive treatment options for severe disease include systemic or local thrombolysis, percutaneous suction or other mechanical thrombus removal techniques, percutaneous transluminal angioplasty with or without stenting, surgical thrombectomy with or without fasciotomy, or a combination of these techniques [20].

Steep leg elevation remains the best method to reduce significant leg edema and should be deployed in conjunction with anticoagulants. The purpose of rapid heparin anticoagulation is to decrease the risk of proximal clot propagation or thromboembolism. Heparin should be initiated with an intravenous bolus of 80–100 U/kg, followed by a continuous infusion of 15–18 U/kg/h and titrated to an activated partial thromboplastin

time (aPTT) goal range of 2–2.5 times the laboratory reference range [21]. With heparin infusion, it is recommended that platelet counts be monitored to allow for early detection of heparin-induced thrombocytopenia. Low-molecular-weight heparins are safe and effective in the treatment of proximal deep venous thrombosis (DVT) and pulmonary embolism (PE); however, there is lesser evidence available to support the use of these agents in phlegmasia and venous gangrene, especially where the potential need for surgical intervention is high [15].

In PCD without gangrene, (1) if no clinical improvement is seen within 6–12 hours, (2) if thrombus burden is significant, or (3) if there is severe symptomatic swelling and tissue ischemia, catheter-directed thrombolysis is employed [15]. Some experts propose catheter-directed thrombolysis directly into the vein with high doses of urokinase or tissue plasminogen activator (t-PA) [12, 22], while others support intra-arterial low-dose thrombolysis via the common femoral artery, reasoning that the arterial route delivers the thrombolytic agent to the arterial capillaries and, subsequently, to the venules, which is seemingly more effective in cases with venous gangrene [20, 23]. There is some debate regarding thrombolysis given that the risk of relevant hemorrhage can be as high as 10–12% [20]; thus, recent reports of therapeutic techniques often involve a combination of direct catheter-based thrombolysis and mechanical thrombectomy [15, 20, 22, 24–26]. Percutaneous transluminal angioplasty with or without stenting has also been used [15, 20] with success though decision for modality and patient selection have not been well illustrated.

Surgical thrombectomy alone is the classically described approach to PCD with massive clot burden and ischemic compromise [19, 27]. However, isolated surgical or catheter-based thrombectomy in combination with heparin anticoagulation in patients with PCD is associated with a high rate of rethrombosis and valvular incompetence or postphlebitic syndrome [12, 23, 28]. Thrombectomy cannot open the small venules that are affected in venous gangrene; thus, a combination of therapies along with thrombolysis is often used for the successful resolution of symptoms [12, 15]. Surgical fasciotomy is indicated in patients with progressive compartment syndrome and venous gangrene. Fasciotomy alone or in conjunction with thrombectomy or thrombolysis reduces compartmental pressures; however, it can significantly increase morbidity because of prolonged wound healing and infection risk [12]. Finally, if all efforts fail, amputation might be required in up to 20% of cases [12].

Key Points

- Phlegmasia may be insidious or fulminant. Most patients presenting with an early form of the disease spectrum (phlegmasia alba dolens) present with symptoms of edema, pain, and blanching (alba) without cyanosis.
- As the disease progresses to phlegmasia cerulea dolens, the blanching caused by subcutaneous edema, venous congestion, and ischemia gives way to progressive arterial compromise leaving the extremity swollen and cyanotic (blue).
- Patients with PCD present with the clinical triad of severe edema, agonizing pain, and cyanosis. Patients with fulminant disease usually present with sudden severe pain, swelling, cyanosis, venous gangrene, and compartment syndrome.
- Ultrasonography, a faster, less expensive, and noninvasive way to assess the venous system, has become a more reliable and accurate way to assess for proximal deep venous thrombosis (DVT) with less morbidity and can be repeated as needed to monitor for thrombus propagation or vessel recanalization.
- The therapeutic intervention for phlegmasia is often multimodal and optimally involves several disciplines. Therapy is aimed at preventing progression to

venous gangrene by reducing venous hypertension and high interstitial pressures through restoring venous outflow to the affected extremity.

- Steep leg elevation remains the best method to reduce significant leg edema and should be deployed in conjunction with anticoagulants. Heparin should be initiated to decrease the risk of proximal clot propagation or thromboembolism with an intravenous bolus of 80–100 U/kg, followed by a continuous infusion of 15–18 U/kg/h and titrated to an activated partial thromboplastin time (aPTT) goal range of 2–2.5 times the laboratory reference range.
- More invasive treatment options for severe disease include systemic or local thrombolysis, percutaneous suction or other mechanical thrombus removal techniques, percutaneous transluminal angioplasty with or without stenting, surgical thrombectomy with or without fasciotomy, or a combination of these techniques.

Pulmonary Embolism

Acute pulmonary embolism is a common diagnosis in the emergency department, and it may present with a wide range of signs and symptoms, from mild dyspnea to sudden and refractory cardiovascular collapse. The diagnosis and treatment of PE cause considerable consternation among EM physicians. Physicians order a substantial number of computed tomography pulmonary angiogram (CT-PA) studies, despite the fact that gestalt, bedside screening metrics, and readily available laboratory tests like d-dimer could obviate some cross-sectional imaging and the concomitant risks [29]. Fortunately, for the majority of patients with a PE, this excess worry is unwarranted. For the patient with a large obstructive burden and marked cardiovascular compromise, minimizing the time to diagnosis and treatment is imperative, as the majority of those patients who die as a result of their PE will do so in the first few hours after the inciting event [30, 31].

Incidence of PE is 69 per 100,000, favoring women in the cohort under 55 years of age, and men in the cohort over 55 years of age [32], and is thought to result in 200,000–300,000 deaths per year. Mortality for untreated PE is up to 30%. With more timely diagnosis and treatment, the mortality can be reduced significantly. The pulmonary embolism severity index (PESI) can be used to predict 30-day mortality, but in patients requiring urgent or emergent evaluation for lysis, it may not be readily available or useful in the decision process (Table 7.1) [33]. Morbidity, in particular, related to the effects of clot burden on RV function and progression to pulmonary hypertension, is a subject of current research interest driving the pursuit of fibrinolysis in patients with signs of right ventricular (RV) compromise but without hemodynamic instability [34–36]. For patients at the far opposite ends of the PE spectrum, for example, those with hemodynamically insignificant PE or cardiovascular collapse, the decision to treat and mode of therapy is based on in the former preventing progression of clot and symptom management, and unloading the RV by relieving clot burden and restoring adequate cardiopulmonary function in the latter.

There are several patient subsets in the emergency department which warrant special regard with respect to PE. In the pediatric population, PE is less common overall than in adults and more common in association with a provoking event or condition, such as a central line, recent cardiac surgery, malignancy, or history of thromboembolic disease [37, 38]. Obstetric populations have an increased incidence of VTE beginning in the first trimester, with a plateau in the second and third trimesters, and a sharp peak immediately postpartum [39–41]. The overall rate of PE is in the postpartum phase is 15 times that of pregnancy, with PE risk concentrated in the first week postpartum, and in mothers over 35 years of age [39, 42]; 96.9% of postpartum PE occurred in the first 6.5 weeks after delivery,

Table 7.1 Pulmonary Embolism Severity Index (PESI) [33]

Criteria	*Score*	*Range*
Age	1 point per year of life	1–100
Gender	Male = 10 points	0 or 10
Heart failure	Active = 10 points	0 or 10
Chronic lung disease	Active or past = 10 points	0 or 10
Heart rate	Heart rate > 110 bpm = 20 points	0 or 20
Respiratory rate	Respiratory rate > 30 bpm = 20 points	0 or 20
Temperature	Temperature < 36 C = 20 points	0 or 20
Oxygenation	Oxygen saturation < 90% = 20 points	0 or 20
Cancer	Active or past = 30 points	0 or 30
Systolic blood pressure	Systolic pressure < 100 mmHg = 30 points	0 or 30
Mental status	Altered mentation = 60 points	0 or 60
Interpretation	*Score*	*Mortality risk*
Class 1	Score < 66	Very low mortality risk (0–1.6%)
Class 2	Score 66–85	Low mortality risk (1.7–3.5%)
Class 3	Score 86–105	Moderate mortality risk (3.2–7.1%)
Class 4	Score 106–126	High mortality risk (4.0–11.4%)
Class 5	Score > 126	Very high mortality risk (10.0–24.5%)

∗Predicts 30-day mortality from pulmonary embolism
∗Risk stratified management
Thrombolytic treatment of massive pulmonary embolism (Class 4–5)
Consider outpatient management for low-risk pulmonary embolism (Class 1)

indicating a rapid return to baseline risk after delivery [39]. Among patients with genetic thrombophilias, factor V Leiden is the most common, and homozygous patients are at significantly increased risk for thromboembolic events [43]. While a PE may be the event that leads to diagnosis, the workup and therapy is the same as for patients with normal factor V activity. This holds true for patients with other genetic thrombophilias except ATIII deficiency, which will be resistant to Heparin. The literature recommends using Heparin for cancer-induced hypercoagulable state (Trousseau's syndrome). Other disease processes associated with PE, such as antiphospholipid syndrome (often associated with Lupus), heparin-induced thrombocytopenia (HIT), paroxysmal nocturnal hemoglobinuria, and sickle cell anemia, can be evaluated and initially treated as any other patient presenting with similar symptoms, with the exception of anticoagulant choice in those patients suspected to have HIT. A history of multiple miscarriages may offer a diagnostic clue in patients with primary or secondary antiphospholipid syndrome. Patients with hepatic dysfunction, specifically cirrhosis, are known to have increased risk of thromboembolic disease, despite relative coagulopathy as indicated by testing such as the international normalized ratio (INR) [44].

Pathophysiology

Thromboembolic disease is characterized by Virchow's triad: hypercoagulable state, alterations in blood flow including stasis and turbulence, and endothelial dysfunction. These three broad categories help explain why the normal equilibrium between clot formation and breakdown may be skewed to favor the formation, propagation, and/or embolization of clots. Small emboli may present with minimal to no symptoms, or they may present with pleuritic chest pain, due to the irritation of the visceral pleura cause by hypoperfusion. Large emboli may cause acutely increased right ventricular and right pulmonary artery pressures. Since the right heart poorly accommodates acute increases in afterload, this may result in relative ischemia, acute right heart failure, cardiovascular collapse, and PEA arrest. It is important to note that while PE is typically thought of as a thromboembolic

phenomenon, any substance that is introduced intravenously and is relatively immiscible in blood can produce similar symptoms. Other embolic phenomenon include fat, amniotic fluid, air, talc (intravenous drug abuse), and iatrogenic emboli, including devices, adhesives, and cements [45–47].

Patient Presentation

There is a reason why physician gestalt ("presence of an alternative diagnosis that was as likely as or more likely than pulmonary embolism") is included in the Wells' criteria for PE [48]; there are no signs or symptoms that are both specific and sensitive to the diagnosis of PE. Despite the absence of a common presentation, experienced clinicians can make reasonable estimations about the presence of this disease state. Perhaps, the most obvious presentation would be the patient with a known acute DVT and no other medical history, who is noncompliant with therapy, and who presents with new-onset dyspnea and pleuritic chest pain. While few patients will present in this way, over three quarters of patients with a PE have evidence of lower extremity deep vein thrombosis (DVT) on clinical examination or imaging [49]. Thus, similar historical risk factors heralding DVT (Table 7.2) are expected in PE. Additional risk factors and historical elements, captured in screening tools like the Wells criteria [48, 50–52], PE Rule Out Criteria (PERC) [53], and Geneva scores [54–56], include oral contraceptive or exogenous estrogen use, hemoptysis, recent intubation, history of DVT/PE, recent fracture, recent surgery, and known hypercoagulable, hemoconcentrated, or hyperviscous states (including polycythemias/leukemias) (Table 7.3) [57, 58]. Common presenting symptoms of PE are nonspecific and can include dyspnea, chest pain, and cough (Table 7.4). Vital signs may be of some assistance and are part of multiple clinical decision rules. Tachycardia, tachypnea, and hypoxia commonly present either singly or in combination with PE;

Table 7.2 Top five most common historical risk factors in patients with confirmed DVT [98]

Risk factors present in patients with DVT	%
>48 h limited mobility in the prior month	45
Recent (<3 months) prior hospitalization	39
Recent surgery	34
Recent malignancy	34
Recent infection	34

Table 7.3 Common clinical scoring systems used in the evaluation of pulmonary embolus

Clinical scoring system	Components
Wells PE risk: 0–1 low, 1–6 moderate, >6 high	Clinical signs and symptoms of DVT = 3 points PE is most or equally likely as a diagnosis = 3 points Heart rate > 100 = 1.5 points Immobilization >3 days, surgery in the prior 4 weeks = 1.5 points Previous, objectively diagnosed PE/DVT = 1.5 points Hemoptysis = 1 point Malignancy with treatment in the prior 6 mo, or palliative = 1 point
Geneva PE risk: 0–3 < 10% incidence of PE, 4–10 intermediate risk, ≥11 high risk >60% incidence of PE	Age > 65 = 1 point Previous PE/DVT = 3 points Surgery required general anesthesia or lower extremity fracture in the prior month = 2 points Active malignancy in prior year = 2 points Unilateral lower extremity pain = 3 points Hemoptysis = 2 points Pain on deep palpation of lower extremity = 4 points Heart rate < 75 = 0 point, 75–94 = 3 points, ≥95 = 5 points
PERC PE risk: if pretest probability is low (<15%), then no further testing is required if none of the criteria are met	Age ≥ 50 HR ≥ 99 O_2 saturation on room air <95% History of venous thromboembolism Trauma or surgery in prior 4 weeks Hemoptysis Exogenous estrogen Unilateral leg swelling

Table 7.4 Common symptoms at presentation in one cohort of patients with confirmed PE [61]

Common presenting complaints in patients with pulmonary embolism	%
Dyspnea	73
Pleuritic pain	66
Cough	37
Leg swelling	28
Leg pain	26
Hemoptysis	13

however, they are hardly specific to PE. On cardiac examination, PE patients may have a split S2 with a prominent P2 due to the effect of elevated pulmonary artery pressure on the pulmonic valve [49]. An extremity, if affected by a DVT, may be tender, swollen, erythematous, or warm to the touch. Fever, if greater than 38° Celsius, or wheezes on pulmonary auscultation are typically indicative of etiology other than PE [59].

Key Points

- The mortality rate for pulmonary embolus exceeds 15% in the first 3 months of treatment, and the majority of deaths due to pulmonary embolism occur in the first 1–2 hours of care.
- Common presenting symptoms of PE are nonspecific and can include dyspnea, chest pain, and cough. Tachycardia, tachypnea, and hypoxia commonly present either singly or in combination with PE.
- The most common arrhythmia seen in PE is sinus tachycardia.

Diagnostics

Once PE enters the differential diagnosis, there are several means to elucidate the diagnosis. There are, as demonstrated by the Wells', PERC, and Geneva scores, a number of historical and exam elements that can be used to generate a pretest probability of PE as a diagnosis. The Wells' score uses physician gestalt in addition to physical findings and historical context, whereas PERC and the Geneva score remove reliance on physician gestalt in an attempt to make application of the criteria more uniform, despite variations in clinician experience [48, 53, 54].

For almost all patients presenting with chest pain or dyspnea, initial evaluation should include a chest radiograph. Plain chest radiography, while frequently abnormal in PE [60], is rarely diagnostic of PE [61]. A normal or mildly abnormal radiograph does help to eliminate other potential diagnoses and will identify patients in whom V/Q scans are likely to be of assistance. Commonly, plain radiographs show nonspecific findings such as atelectasis and small pleural effusions. Uncommon plain radiographic findings more strongly associated with PE (but not diagnostic) are as follows: The Westermark sign, which is the absence of pulmonary vasculature consistent with pulmonary artery hypoperfusion or vasoconstriction; Hampton's hump, which is a dome-shaped peripheral density consistent with infarction and subsequent localized hemorrhage; and the Fleischner sign, which is the dilation of the central pulmonary artery seen in some patients with elevated pulmonary artery pressures [61]. In patients at risk for underlying cardiac etiology of their symptoms, an EKG will be of some assistance. EKG findings concerning for and consistent with PE include sinus tachycardia, the famed but uncommon S1Q3T3, a new right bundle branch block, a new rightward axis, or pulseless electrical activity (PEA) arrest [62].

Laboratory studies (Table 7.5), though nonspecific for PE, can help identify other etiologies and establish whether or not renal function is sufficient to tolerate contrasted CT for PE. While

Table 7.5 Common laboratory abnormalities associated with pulmonary embolus

Laboratory study	Abnormality
CBC	Normal, leukocytosis
BMP	Normal
ABG	Normal, respiratory alkalosis, hypoxemia, increased A-a gradient
d-dimer	Elevated
BNP	Normal, elevated (right heart strain)
Troponin	Normal, elevated (right heart strain)

contrasted angiography might be avoided in at risk patients, it might be worth considering in those patients with high-risk features that might benefit from early aggressive care. Additionally, laboratory studies in suspected PE may be used to support the diagnosis and further classify PE. Laboratory studies ordered in evaluation of a potential PE patient may reasonably include a complete blood count, basic metabolic panel, troponin, brain natriuretic peptide, arterial blood gas, and a d-dimer. D-dimer has a significant role in PE with the exception of rare false negatives; it is highly unlikely that a patient with a negative, or normal, d-dimer has a PE [63]. The converse, however, is not true, and many patients with an abnormal d-dimer do not have a PE as many common conditions presenting similarly to PE can elevate d-dimer levels (e.g., aortic dissection). Age and pregnancy can also alter d-dimer values in a predictable sequence [64]. Hence, a d-dimer should not be ordered casually, as a positive test, might necessitate further explanation and three-dimensional imaging.

Direct visualization of a PE is ideal and is the only way to definitely diagnose a PE. Computed tomography with a timed contrast bolus corresponding to opacification of the pulmonary arteries (CT-PE) provides optimal visualization [65]. CT-PE, however, bears significant radiation and contrast burdens, both of which have potential long-term consequences. Patients who receive a CT-PE have a nearly 40% chance of having a subsequent CT within 2 years [66], and the oncogenic and nephrotoxic risks of repeated exposures are significant [67, 68]. Pulmonary angiography, ventilation/perfusion (V/Q) scanning, and lower extremity venous Doppler are alternative testing modalities, but do not offer definitive confirmation. Pulmonary angiography carries similar risks as CT-PE, and the number of practitioners and facilities equipped to perform and evaluate these studies is decreasing. V/Q scanning is a reasonable alternative in the patient with a previously normal chest radiograph [69], and it may be the preferred chest imaging modality in pregnant patients, if imaging is indicated. Additionally, for pregnant patients or in patients with contrast contraindications, d-dimer and lower extremity duplex might serve as first-step strategies. Some argue that if both the d-dimer and the Dopplers are positive, then there is no need for confirmatory chest imaging, and the patient can be started on therapeutic anticoagulation [64]. If, however, the Dopplers do not reveal an extremity deep vein thrombosis, then chest imaging is indicated, and V/Q, as mentioned, might be the preferred imaging modality [64]. Magnetic resonance angiography is an alternate diagnostic modality if the facility is equipped to perform and evaluate such a test [70], but image quality limits use in a significant number of patients.

Echocardiography, while not always providing direct visualization of the clot within the right ventricle or pulmonary artery, can help identify patients with significant clot burden, right ventricular dilation, and contractile dysfunction. Transthoracic echocardiography can be obtained formally, though a finalized read of that study may not be available in a timeframe necessary to support diagnosis or therapy decisions. For those practitioners comfortable with limited bedside echocardiography, a parasternal short-axis view demonstrating paradoxical septal bowing (toward the left ventricle), septal flattening, and/or evidence of right ventricular volume overload (RV diameter $\geq$ LV) are indicative of significant clot burden and impending hemodynamic compromise. Echocardiography can also identify a potential alternative diagnosis like pericardial effusion. Coupling the cardiac evaluation with pulmonary and DVT ultrasonography dramatically improves the sensitivity and specificity of bedside diagnosis for PE [71].

Key Points

- Because the symptoms of PE can be vague and can mimic other diseases, several clinical scoring systems (e.g., Wells', PERC, and Geneva scores) have been developed to generate a pretest probability of PE as a diagnosis and to help guide further intervention.

- ECGs can be normal in 10–15% of PE patients but are useful to determine other underlying cardiac etiologies of patient symptoms.
- Chest radiographs are rarely diagnostic though are abnormal in 76–90% of PE patients. A normal or mildly abnormal radiograph does help to eliminate other potential diagnoses and will identify patients in whom V/Q scans are likely to be of assistance.
- Bedside ultrasound can provide information regarding cardiac performance and delineate possible differential diagnoses. A parasternal short-axis view demonstrating paradoxical septal bowing (toward the left ventricle), septal flattening, and/or evidence of right ventricular volume overload (RV diameter ≥ LV) are indicative of significant clot burden and impending hemodynamic compromise.
- Right ventricular (RV) dilation can easily be determined by left ventricular (LV) comparison in the subcostal or apical view.
  - RV size = LV size: moderate RV dilation
  - RV size > LV size: marked RV dilation

Medical Therapy

The medical and interventional strategies in PE can best be stratified by subgroups that are based on the severity of the PE and by acute and subacute strategies of therapy [72]. Traditionally, PE has been classified based on the character of the hemodynamic stability and clot burden. Treatment approaches for PE subtypes vary based on the severity of patient illness making practitioners more likely to deploy high-risk therapies in those patients with significant cardiopulmonary compromise and more likely to die from their PE. In the medical literature, PE has traditionally been classified as either "massive" (with hemodynamic instability), "submassive" (now termed intermediate-risk PE), or "nonmassive" though the definitions vary and can be ambiguous [72]. For the EP, it is important to know how to manage the acutely ill PE patient, understand the goals of treatment, and command the varied options for management. The overall goal of therapy is not only to stabilize the acutely ill patient and reduce mortality but also to also prevent downstream sequella of PE, such as right ventricular (RV) dysfunction, right heart strain, and chronic thromboembolic pulmonary hypertension (CTEPH) [72–74].

Goldhaber and Lualdi first described acute pulmonary embolism as a spectrum of six syndromes: the first two syndromes, "massive PE" and "moderate-to-large PE," apply to patients with substantial pulmonary perfusion defects and right ventricular dyskinesis [75]. These two can be distinguished from one another by a transition from relatively normal blood pressures (moderate-to-large PE; 30% perfusion obstruction) to persistent arterial hypotension (massive PE; >50% obstruction) [75]. Thus, "massive" from "submassive" pulmonary emboli can be distinguished on the basis of hemodynamic stability, and the use of this distinction is often used as part of an overall strategy for risk stratification and treatment [76].

Massive PE (MPE) is best defined by consensus as an "acute PE with sustained hypotension (systolic blood pressure <90 mm Hg for at least 15 minutes or requiring inotropic support, not due to a cause other than PE, such as arrhythmia, hypovolemia, sepsis, or left ventricular [LV] dysfunction), pulselessness, or persistent profound bradycardia (heart rate <40 bpm with signs or symptoms of shock)" [72]. MPE with shock is one of the more anxiety-provoking conditions seen in the ED and is a condition that carries a high mortality despite optimal care [43, 72]. Diagnosis alone can be challenging, thus familiarity with the optimal management of these unstable patients should optimize delivery of time-dependent therapy.

Resuscitation and Initial Cardiopulmonary Stabilization

Patients with MPE often present with moderately marginal to persistently unstable hemodynamics. Initial efforts should be aimed at stabilizing the patient by utilizing a combination of fluids, vasopressors, and inotropic agents. The initial reaction of the EP to hypotension in most cases is to begin with a fluid bolus, regardless of an assessment of the patient's fluid status. However, the use of fluid loading in acute massive pulmonary embolism remains controversial. Though fluids might initially improve blood pressure response, the added strain on the right heart in the form of increased end-diastolic volume may actually serve to worsen RV failure. Therefore, current literature supports a 250- to 500-ml bolus and the avoidance of excessive fluid resuscitation in the absence of a clear understanding of the patient's right heart physiology [77].

Hypotension in MPE is the result of RV outflow obstruction leading to poor pulmonary perfusion and circulatory collapse secondary to RV strain and right-sided heart failure. Though vasoconstriction may seem counterintuitive; it is important to realize that the RV is perfused in both diastole and systole [78, 79]. Therefore, in the setting of shock with increased myocardial oxygen demand, maintaining the mean arterial pressure head can improve myocardial perfusion and hibernating RV function. In MPE, the ideal agent would increase systemic vasoconstriction without increasing pulmonary vascular resistance, though no currently available agent achieves this goal. Data extrapolated from animal models and case studies suggest that norepinephrine (NE) is the vasopressor of choice for shock secondary to MPE [77, 80–85]. Epinephrine as a second-line agent has been advocated in case-based literature for treatment of refractory shock complicating PE [86], and vasopressin has also been used in low doses to treat hypotension without detriment to cardiac output or pulmonary artery pressures [87]. Often, a single vasopressor is insufficient to overcome the hemodynamic instability seen in massive PE; thus, a combination of vasoactive agents (Table 7.6) is often needed. Of the available inotropes, dobutamine is considered the inotropic agent of choice for the treatment of PE-related cardiac failure. Dobutamine beta-adrenergic positive inotropic and pulmonary vasodilating properties lead to increased right ventricular contractility and decreased pulmonary vascular resistance [77].

Table 7.6 Common vasoactive agents used in pulmonary embolism management

Vasoactive agent	Dosing
Norepinephrine	2–30 mcg/min
Epinephrine	2–10 mcg/min
Vasopressin	0.01–0.04 u/min
Dobutamine	2–20 mcg/kg/min

Key Points

- Hypotension can be managed with a small fluid bolus (250–500 ml) to avoid complicating RV failure and followed with the addition of vasopressors (norepinephrine) in those patients with ongoing hemodynamic instability.
- Epinephrine and vasopressin as well as dobutamine can be considered in refractory hypotension.

While supplementary oxygen is practical in all patients with pulmonary compromise, the oxygen debt and respiratory distress in MPE often necessitate more advanced pulmonary support. The EP must approach the respiratory support of the patient with MPE with some degree of caution as negative interactions between the heart and lungs can further destabilize an already unstable situation. Positive-pressure ventilation alters thoracic physiology and may decrease venous return to the heart and further increase right heart pressure and systolic dysfunction.

Intubation in MPE can be complicated by cardiovascular collapse for several reasons. Sedatives can blunt catecholamine-directed peripheral vasoconstriction and central pulmonary vasodilation. Lung overinflation can

increase pulmonary vascular resistance and decrease venous return. Thus, EPs considering rapid sequence intubation in MPE should consider sedative agents that preserve hemodynamic function (i.e., etomidate and ketamine), select ventilator settings that limit overinflation, and have vasopressors immediately available or already infusing in preparation for worsened hypotension.

Mechanical ventilation, often a necessary adjunct in the management of patients with MPE, can lead to elevated airway pressures, increased transpulmonary pressures, decreased venous return, limited RV diastolic filling, and increased RV afterload that impedes RV systolic function [88, 89]. Limiting positive end-expiratory pressure (PEEP; 5 cm H_2O) and tidal volumes (6–8 ml/kg) might decrease airway pressures and minimize RV dysfunction. Ventilation management strategies must be tailored to limit hypercarbia and hypoxemia, which can exacerbate pulmonary vasoconstriction and hypertension if adequate ventilation or oxygenation is not maintained. Close monitoring and fine-tuning of tidal volume and respiratory rate can help maintain normocarbia, while the maintenance of recruitment (PEEP) and modulation of gas trapping (expiratory time) can improve oxygenation [81, 88, 90].

Key Points

- Supplemental O_2 should be used to treat hypoxia/hypoxemia secondary to shunting.
- NIPPV/ventilation may be necessary in patients suffering from acute PE with a goal of using low tidal volume and low peep ventilation to avoid further altering hemodynamics.
- Prepare for worsened hypotension with intubation and ventilation; it is often necessary to have vasopressors immediately available or already infusing when preparing for induction.
- Avoid lung hyperventilation as this can worsen hemodynamic instability.

Clot Management

Beyond the acute management of the hemodynamic stability and potential respiratory failure seen in PE, the treatment of the pulmonary embolism itself is controversial. Fibrinolytics, the mainstay of acute PE treatment, act directly on the clot itself promoting hydrolysis of fibrin and leading to clot break down [72, 74]. There is a general consensus that the use of fibrinolytics in the critically ill, hemodynamically unstable patient with pulmonary embolism, in the absence of major contraindications, is recommended (Class IIa, Level of Evidence B) [72]. A meta-analysis and formal Cochrane Review strongly endorse the use of rapid fibrinolytic therapy versus the use of heparin alone as a means to potentially reduce recurrence (OR 0.63; 95% CI 0.33–1.20) and death (OR 0.89; 95% CI 0.45–1.78) in MPE [91]. For the EP, administration of rapid fibrinolytic therapy is less invasive and is the primary method of treatment for the hemodynamically unstable PE patient who lacks contraindications to systemic therapy. Three thrombolytic agents are currently approved for use in patients with acute PE: streptokinase, urokinase, and rt-PA (Table 7.7). A 2005 meta-analysis aimed at identifying differences among thrombolytic regimens failed to demonstrate any statistically significant differences in efficacy [92]. Despite the lack of data proving superiority, the American College of Chest Physicians (ACCP) guidelines suggest using the thrombolytic regimen with the shortest infusion time (currently Alteplase) [21, 93].

The EP is more likely through the course of his or her career to encounter the patient with submassive (intermediate risk) PE in whom the treatment

Table 7.7 Thrombolytic regimens for acute pulmonary embolism

Drug	Dosing regimens
Alteplase (rt-PA)	Initial dose: 10 mg bolus, then infusion: 90 mg over 2 h
Streptokinase	Initial dose: 250,000 units over 30 min, then infusion: 100,000 units/h over 24 h
Urokinase	Initial dose: 4400 units/kg over 10 min, then infusion: 4400 units/kg/h over 12 h

options can be varied and sometimes controversial. This patient, unlike the hemodynamically compromised patient, often presents normotensive with minimal to no respiratory distress and often appears less sick. The optimal treatment strategy is less clear in submassive PE. The EP treatment choices include the use of supportive measures and therapeutic anticoagulation, alternative anticoagulants such as Xa inhibitors, in some cases systemic fibrinolytics (in full or altered doses), and in some institutions referral for catheter-directed fibrinolysis or direct clot extraction.

The most widely accepted initial management for submassive PE is anticoagulation with either unfractionated heparin or low-molecular-weight heparin (LMWH) [72] aimed at reducing further clot propagation and preventing additional VTE. Early anticoagulation is suggested in PE regardless of downstream management style, as it remains a relatively low risk and is an easily titratable and reversible treatment (Table 7.8). The decision to pursue fibrinolysis should not delay the onset of anticoagulation as it can be held for fibrinolysis delivery and restarted after the completion of lytic therapy. For many community EPs, basic anticoagulation will be the mainstay of treatment as it easily initiated and followed by the initiation of oral anticoagulants (OACs), though anticoagulation often requires hospital admission. Heparin therapy can be initiated with a bolus or without. In patients without contraindications, a bolus of heparin (80 u/kg) should be given followed by a titratable infusion (18 u/kg/h initially and then adjusted to a goal aPTT of two times the normal reference range).

One of the more controversial treatment options includes the use of systemic fibrinolysis for submassive PE. Fibrinolysis in submassive PE in recent research has been focused on evaluating the efficacy of early fibrinolysis at mitigating unwanted debilitation and chronic complications resultant from chronic RV remodeling and pulmonary artery hypertension in VTE [35]. Specifically, the MOPETT trial found that a lower dose (50 mg) of TPA was as efficacious in reducing PA pressures as the traditional 100-mg dose (better than the use of LMWH alone) and did not show an increased risk of major bleeding (including intracranial hemorrhage) in their treatment group [36]. What remains controversial is whether or not the risk of major bleeding outweighs the potential benefits seen in reducing downstream debilitation that can accompany PE. EPs should be aware that fibrinolysis is a reasonable option (including lower doses) and that this option might best apply in the "borderline" patient without hemodynamic compromise but who demonstrates signs of acute right heart dysfunction. Additionally, patients above the age of 75 are at higher risk of bleeding and might benefit from reduced dose fibrinolysis [72, 94]. Ultimately, the submassive patient who is stratified as high risk for chronic VTE-related cardiopulmonary compromise should be involved in the decision-making process and the bleeding risks reviewed prior to using fibrinolysis.

In the extremely low-risk group, recent PE research suggests that patients with segmental and nonobstructing submassive PE might easily be managed with outpatient regimens [95–97]. For those patients who present with minimal symptoms, and without evidence of right heart strain, the relatively new Xa inhibitors are a reasonable option. They may be used in conjunction with a

Table 7.8 Anticoagulants used in the treatment of venous thromboembolic disease

Anticoagulant	Initial dose	Restriction	Time to peak
Unfractionated heparin	17 U/kg then 70 U/kg/hr, IV	Heparin-induced thrombocytopenia	1 hour
Enoxaparin	1 mg/kg subcutaneously[a]	Creatinine clearance <30 ml/min	3 hours
Dalteparin	200 U/kg subcutaneously[a]	Creatinine clearance <30 ml/min	4 hours
Fondaparinux	5–10 mg subcutaneously[a]	Creatinine clearance <30 ml/min	3 hours
Rivaroxaban	15 mg orally with food	Creatinine clearance <30 ml/min	2–4 hours
Apixaban	10 mg orally with or without food	Creatinine clearance <30 ml/min	3–4 hours

[a]Although low-molecular-weight heparin compounds are usually injected subcutaneously, no trials have been conducted to justify this route over intravenous injection. Intravenous injection achieves more rapid anticoagulation and does not produce more bleeding.

single therapeutic dose of LMWH, such as enoxaparin and confer immediate anticoagulation.

Several of the Xa inhibitors, also known as the novel oral anticoagulants (NOACs), are now FDA approved for the management of acute PE and are easy to use without the need for titration or outpatient monitoring. Thus, these agents are ideally suited for the low-risk PE patient who could potentially be discharged from the ED.

The remaining available therapies, such as catheter-directed fibrinolysis or thrombectomy and clot extraction, are becoming increasingly available in larger institutions. These therapies may be the best option in moderately ill PE patients for whom bleeding risks are too great. Thus, these novel interventional approaches in a complex patient subtype might require patient transfer to another institution. The focus of optimization and advanced technique availability has fueled recent discussion as to whether "PE Centers" are needed to impart best available practices.

Key Points

- UFH/LMWH should be initiated as soon as the dx of PE is suspected. It can be stopped to administer fibrinolytics and resumed following.
- Submassive PE treatment options are varied, including the potential outpatient management with NOACs, patient transfer to specialty centers for advanced therapies, and the use of altered doses of fibrinolytics in the borderline patient.

Summary

Complex venous thromboembolic disease requires rapid evaluation, diagnosis, and management. It is clear that the clinician with an understanding of the pathophysiology of complex VTE can better guide therapy according to clinical acumen. Beginning resuscitation and escalating support while initiating definitive therapy are the mainstays of ED care. Finally, heparinization and thrombolytic therapy play an essential role in the successful treatment of the patient with complex VTE. The EP armed with a standardized approach to therapy in VTE will likely play a key role in limiting patient morbidity and mortality.

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