Venothromboembolism

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Venothromboembolism (VTE) represents a spectrum of pathology from simple superficial thrombophlebitis to fatal pulmonary embolus (PE). It was first depicted in the thirteenth century, but was not described in the medical literature until the late 1600s [1,2]. In 1916, VTE became a treatable disease with the discovery of heparin. The presence of an effective therapy heightened the importance of diagnosing VTE, fueling a plethora of medical research and technologic developments over the next century. Despite advancements, VTE remains an elusive entity because of atypical presentations and associated diagnostic challenges.

In the mid to late twentieth century, autopsy and inpatient studies found PE was often deadly with an untreated mortality of 26% to 30% [3–5]. Up to 70% of PEs were diagnosed on autopsy that had not been suspected clinically [6]. The high frequency of missed diagnosis and mortality has since led clinicians aggressively to seek and treat this disorder. Recently, some authors suggest the incidence of VTE is lower in the emergency department (ED) population and may be less clinically significant than inpatient VTE [7]. Studies of ambulatory patients who did not receive anticoagulation for VTE failed to document negative outcomes of death or thrombus progression, challenging the idea that anticoagulation is beneficial to all patients with VTE [8,9]. Interestingly, heparin was accepted as the standard of care without studies validating its efficacy. A growing school of thought suggests that although PE is certainly fatal in some patients, it is a normal physiologic event in others that does not require treatment, and aggressive searches will likely identify patients with clinically insignificant VTE [7]. Unfortunately, no methods yet exist to identify patients who can safely be managed without anticoagulation.

Whether clinically significant or not, the occurrence of missed deep venous thrombosis (DVT) and PE is high [10,11], and when it is clinically

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suspected it is diagnosed only 20% to 35% of the time [12,13]. Classic presentations occur less frequently than atypical presentations and asymptomatic VTE is common. One recent study found 6.3% of cancer patients had asymptomatic VTE on routine imaging [14]. Furthermore, silent PE is present in approximately 40% to 60% of patients who present with DVT [8].

**Epidemiology**

Because of the high rate of missed diagnosis, the true incidence of DVT and PE is unknown. In the United States, it is estimated that first-time VTE occurs in approximately 100 per 100,000 persons per year with approximately one third of cases caused by PE and two thirds of cases caused by DVT. There is no significant difference between men and women [15]. The incidence increases dramatically with age from less than 5 cases per 100,000 persons under the age of 15 to approximately 500 cases per 100,000 persons over the age of 80 [16,17]. The rate seems to increase sharply after age 45 [18]. Venous valve incompetence with increased venous stasis, sedentary lifestyle, and acquired comorbidities are some of the theoretic etiologies for the increased incidence with age. Other epidemiologic factors associated with increased incidence include white and African American race [19] and winter months [20].

**Pathophysiology**

The spectrum of VTE begins with formation of a thrombus. In 1686, the surgeon Richard Wiseman suggested thrombus formation was related to coagulation of the serum, thickening of the blood, or venous obstruction, and recognized the high prevalence of VTE in both pregnancy and malignancy [2]. Rudolf Virchow [21] was later credited with the classic triad associated with VTE: stasis, endothelial injury, and hypercoagulability. When present, these factors disrupt the balance between endogenous fibrinolysis and fibrin formation contributing to the formation and propagation of thrombus. Vascular injury initiates release of tissue factor that activates factor Xa and leads to increased fibrin formation and deposition. Hypercoagulable states also offset the balance of the natural clotting cascade in favor of fibrin production and clot formation. Finally, venous stasis allows for increased fibrin cross-linking [22]. Clinical states that involve the presence of Virchow’s triad result in a higher incidence of VTE (Box 1) [18,23,24].

**Deep vein thrombosis**

Although thrombosis can occur anywhere in the venous system, it typically forms at locations of injury or stasis, particularly in the valve cusps in the venous sinuses of the calf veins [25]. Approximately 90% of DVTs
occur in the lower extremities, but only thrombus from deeper and more proximal vessels are believed to embolize to the lungs. For this reason, the venous system is divided by proximity and depth. In the lower extremity, the superficial system is comprised of the greater and short saphenous veins (Fig. 1). The deep veins are divided into proximal and distal. The distal deep veins include the anterior tibial, posterior tibial, and peroneal veins (collectively called the calf veins). The proximal deep veins include the popliteal, superficial femoral, deep femoral, common femoral, and external iliac veins. A DVT is classified as distal if it is below the knee (also called a calf DVT) and proximal if it is located in the popliteal vein or above. Although distal DVTs are generally not thought to pose an immediate threat to embolization, there is a 20% to 30% incidence of propagation to the proximal venous system [26]. Clinically significant thrombosis can also involve pelvic veins, upper extremity veins, and venous sinuses of the skull.

Clinical presentation

The history and physical examination are helpful in suggesting the diagnosis, but no one sign or symptom in isolation maintains significant sensitivity or specificity for DVT [27]. Symptoms can include a sense of fullness, paresthesia, or pain in the calf or thigh. Physical examination may show unilateral leg edema, erythema, warmth, tenderness, or a palpable cord.
The classic Homan’s sign (sharp calf pain on passive dorsiflexion of the foot) has proved to be insensitive and nonspecific [28]. Although symptoms are less frequent with smaller and more distal clots, large proximal clots may also be asymptomatic in the presence of adequate collateral veins and patency of vessels [24]. The clinical signs and symptoms of DVT are often found in many other conditions affecting the lower extremity including musculoskeletal injuries, cellulitis, ruptured Baker’s cyst, vasculitis, congestive heart failure, lymphedema, and other nonthrombotic conditions. Laboratory and radiologic testing are fundamental in the diagnosis of DVT.

**Ultrasound**

Ultrasound is the test of choice for diagnosis of DVT. It is fast, accurate, and readily available in most EDs. Since the 1990s, ultrasound has replaced venography as the gold standard for DVT evaluation. Ultrasound provides nearly equal diagnostic information while avoiding the risks of invasive venography, which has a 2% chance of inducing DVT [29].

The two methods of ultrasound commonly used when assessing DVT are compression and duplex. Compression ultrasound works by the principle that normal veins collapse when extrinsic pressure is applied by the sonographer. When a vein fails to collapse, it indicates the presence of an intravascular mass (thrombus by default) (Figs. 2–4).
Duplex ultrasound is compression ultrasound with the addition of spectral and color flow Doppler to assess respiratory variation and augmentation. In contrast to compression ultrasonography that is easily learned and can be quickly performed by clinicians in the ED, duplex is relatively complicated, time consuming, and expensive. Despite these characteristics, it adds little to compression ultrasonography in the diagnosis of DVT (Table 1) [30–39].

When performing compression ultrasonography, assessment of the entire proximal venous system is unnecessary to rule out proximal DVT. In a study of 562 venograms performed on patients with DVT, no cases of isolated superficial femoral or pelvic vein thrombosis were identified. All DVTs

Fig. 2. Compression ultrasonography in normal lower extremity. Popliteal vein (arrows) collapses with compression (right). (Courtesy of Anthony J. Dean, MD, Philadelphia, PA.)

Fig. 3. Compression ultrasonography of DVT in the common femoral vein. Vein (V) does not collapse with compression (right) indicating presence of DVT. (Courtesy of Anthony J. Dean, MD, Philadelphia, PA.)
involved either the popliteal, common femoral, or both veins [40]. This has led to the development of limited compression ultrasonography (LCUS). LCUS is compression ultrasonography focused on the common femoral and popliteal veins. Despite rare case reports of isolated superficial femoral DVTs, studies have demonstrated the safety of withholding anticoagulation after negative LCUS [41,42]. It should be noted that LCUS is insensitive for calf DVTs and repeat ultrasonography in 7 days is recommended in certain high-risk patients (see later).

Many clinicians, including emergency physicians (EPs), are performing bedside ultrasonography to evaluate for DVTs. Jolly and colleagues [43] were the first to demonstrate the ability of EPs to perform color Doppler

Table 1
Performances of various ultrasonography methods for proximal deep venous thrombosis

<table>
<thead>
<tr>
<th>Ultrasonography method</th>
<th>% Sensitivity</th>
<th>% Specificity</th>
<th>% PPV</th>
<th>% NPV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duplex [31–33]</td>
<td>95–100</td>
<td>91–100</td>
<td>96–100</td>
<td>97–100</td>
</tr>
<tr>
<td>Compression [34–36]</td>
<td>93–100</td>
<td>96–100</td>
<td>99–100</td>
<td>92–100</td>
</tr>
</tbody>
</table>

*Abbreviations: NPV, negative predictive value; PPV, positive predictive value.*
ultrasonography successfully in a retrospective observational analysis in 1994. Two EPs performed ultrasounds in the ED after training in a vascular laboratory (performing 25–30 studies each). The sensitivity and specificity of their color Doppler ultrasounds for acute DVTs were 100% (seven of seven) and 75% (six of eight), respectively. The two false-positives were patients with old DVT. In 1999, Frazee and colleagues [44] prospectively demonstrated a 95.7% negative predictive value (NPV) of EP-performed LCUS.

Although accurate, EPs can also maintain their goal of rapid throughput by performing LCUS. Blaivas and colleagues [45] demonstrated a median examination time of 3 minutes and 28 seconds of EP-performed LCUS, while maintaining a 98% correlation with vascular laboratory–performed studies on the same patients. Another study by Theodoro and colleagues [46] observed a 125-minute reduction in time to patient disposition with EP-performed US compared with radiology-performed US while also maintaining good correlation. Jang and colleagues [47] prospectively studied the ability of eight emergency medicine residents with minimal training in LCUS and found a sensitivity and specificity of 100% and 91.8%, respectively, with an average scan time of 11.7 minutes.

Recently, Maggazini and colleagues [48] demonstrated that full duplex scanning can also be performed effectively by EPs. After a 30-hour training course, five EPs performed duplex ultrasound on 399 patients who then had formal vascular scanning within 24 hours. EPs achieved a NPV of 100% and a positive predictive value of 95%. Although average study time was longer at approximately 10 minutes, the authors suggest that this is still more efficient than having the patient return for a repeat examination in 7 days (as recommended with LCUS) and avoids issues of failure to follow-up. Regardless of full versus limited studies, EP-performed ultrasonography may be particularly valuable in EDs without around-the-clock access to trained ultrasound technicians. Criticisms of ultrasonography include its inability to distinguish acute versus chronic DVT, decreased accuracy in obese patients, and lack of availability in some institutions.

**Other imaging modalities**

The traditional gold standard diagnostic modality for DVT was contrast venography, which yields a 99% to 100% sensitivity and specificity [49]. This invasive test is rarely performed because of high demand of resources and associated complications [50].

CT venography (CTV) is a diagnostic modality that evaluates the pelvis, thighs, and calves after injection of venous phase contrast material. It has near equal sensitivity and specificity to ultrasound for diagnosing proximal DVT [51]. Because CT angiography (CTA) of the pulmonary vessels and CTV can be performed simultaneously, CTA-CTV is an attractive option for patients with concern for both DVT and PE. Furthermore, CTV can diagnose pelvic and calf DVTs. Cost, radiation exposure (particularly
through the reproductive organs), intravenous contrast exposure, and need for intravenous access are ongoing concerns about the use of CTV.

Magnetic resonance venography is another attractive alternative for diagnosis of DVT. It is highly accurate with a sensitivity of 100% and specificity of 98% to 99% for pelvic and proximal DVTs. It is less reliable for calf DVTs (sensitivity 68%), but often provides an alternative nonthrombotic diagnosis [52]. MRI is able to distinguish between acute and chronic DVTs. As opposed to CT, pelvic and lower-extremity MRI is considered safe in pregnancy. Cost and availability have limited the use of magnetic resonance venography in clinical practice.

Impedance plethysmography is a noninvasive test that estimates blood volume by measuring changes in electrical resistance in a targeted area of the body. Although it can be used to diagnose DVT, impedance plethysmography is less favorable in the ED and other clinical settings because of lower sensitivity when compared with LCUS, common interobserver disagreements, and lack of availability [35,53].

**D-dimer**

D-dimer is an end product of clot lysis. Its presence signifies the existence of thrombus with an active deposition and degradation of cross-linked fibrin by plasmin [22]. Small amounts of D-dimer are normally present in the serum; however, elevated D-dimer levels correlate with increased thrombus volume. The D-dimer test does not discriminate between physiologic (eg, postoperative or posttrauma) and pathologic (eg, deep vein) thrombus. D-dimer levels may also be elevated in cancer, late pregnancy, recent trauma or surgery, sepsis, and many other medical conditions, limiting its use [54]. For these reasons the D-dimer is a sensitive, but nonspecific test. Many clinical algorithms have incorporated D-dimer testing as a way to rule out DVT and prevent the need for further imaging [55–59].

There are currently three main ways of detecting D-dimer levels in the bloodstream: (1) ELISA, (2) latex-agglutination, and (3) whole-blood agglutination. The ELISA test is the gold standard, yielding 95% sensitivity and 45% specificity for PE and a 94% sensitivity and 43% specificity for DVT. A typical 4-hour turnaround time, however, hinders the use of ELISA in the ED [60]. Rapid ELISA tests, however, are suitable for ED use. They perform similarly to standard ELISA and can be run in 35 minutes [60].

First-generation latex-agglutination tests are inexpensive and rapid, but lack adequate sensitivity for ED testing [61]. Newer second-generation latex-agglutination tests use immunoturbidimetric techniques and demonstrate sensitivity profiles similar to ELISA. Studies of second-generation latex-agglutination D-dimer tests have been used in low- and intermediate-risk patients to exclude VTE [56,57].

Whole-blood agglutination tests are qualitative tests that change color when D-dimer is bound by a monoclonal antibody that is linked to another
monoclonal antibody, binding red blood cells. Whole-blood agglutination is rapid and inexpensive, but is criticized for being operator dependent. Sensitivity and specificity are approximately 87% and 68%, respectively, but it has been combined with low pretest probability scores to achieve high NPVs successfully for VTE [58].

Appropriate use of D-dimer testing in VTE hinges on understanding the concepts of pretest probability, likelihood ratio, and posttest probability. In the example of VTE and D-dimer, the pretest probability is the chance that the patient has VTE before D-dimer testing. The posttest probability is the chance of disease after testing. The negative likelihood ratio (NLR) is a factor that when applied to the pretest probability yields the posttest probability given a negative D-dimer. Each D-dimer test has a different NLR and yields different posttest probabilities for a given pretest probability (Table 2).

Before obtaining a D-dimer test, the clinician should determine whether a negative result yields a posttest probability acceptable for excluding VTE. This requires an understanding of the patient’s pretest probability and the NLR of the D-dimer test being used. Most studies that validate D-dimer testing focus on patients with a low pretest probability and implement a D-dimer test with a strong NLR [55,57–59,62–65]. D-dimer tests maintain a higher specificity if used in appropriate patient populations, such as younger, otherwise healthy people, without comorbid conditions or late pregnancy.

Causes for a false-negative D-dimer test include small amounts of thrombus, old thrombus, and impaired fibrinolysis. D-dimer levels correlate with the amount of thrombus surface area participating in active fibrinolysis. For this reason, D-dimer testing is often negative with smaller thrombi, as is seen with distal DVTs [66,67]. Older clots tend to stabilize with cross-linked fibrin and may produce little or no D-dimer. D-dimer levels may normalize as early as 7 days after clot formation [68]. Finally, acute thrombus may not generate D-dimer in patients with impaired endogenous fibrinolysis [69].

Clinical pathways

Although the diagnosis of DVT by physical examination alone is inadequate, performing radiologic testing on all patients is unnecessary. Furthermore, performing serial ultrasonography on all patients is inefficient because only 1% to 2% of patients have proximal DVT on repeat imaging after initial negative ultrasound [70,71]. In 1995, Wells and colleagues [36] discovered that implementation of clinical prediction rules to assess a patient’s pretest probability could reduce the need for formal radiologic studies to rule out DVT. In 1997, Wells and colleagues [72] demonstrated that a single negative LCUS was sufficient to rule out DVT in low-risk patients. In 2003, Wells and colleagues [58] showed that a negative whole-blood agglutination or immunoturbidimetric D-dimer test eliminated the need for ultrasound in low- and intermediate-risk patients. Although a negative D-dimer test does not eliminate the need for ultrasound in the high-risk population, it did predict
Table 2
Negative likelihood ratios of various D-dimer tests

<table>
<thead>
<tr>
<th>D-dimer</th>
<th>Deep vein thrombosis</th>
<th>Pulmonary embolus</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>NLR (95% CI)</td>
<td>Post-test probability</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Given (-) D-dimer</td>
</tr>
<tr>
<td>ELISA</td>
<td>0.15 (0.07–0.30)</td>
<td>3.6</td>
</tr>
<tr>
<td>Quantitative rapid ELISA</td>
<td>0.08 (0.02–0.38)</td>
<td>2</td>
</tr>
<tr>
<td>Semiquantitative rapid ELISA</td>
<td>0.21 (0.10–0.42)</td>
<td>5</td>
</tr>
<tr>
<td>Qualitative rapid ELISA</td>
<td>0.13 (0.06–0.32)</td>
<td>3.1</td>
</tr>
<tr>
<td>Quantitative latex</td>
<td>0.21 (0.12–0.38)</td>
<td>5</td>
</tr>
<tr>
<td>Semiquantitative latex</td>
<td>0.31 (0.21–0.47)</td>
<td>7.2</td>
</tr>
<tr>
<td>Whole-blood agglutination</td>
<td>0.25 (0.18–0.36)</td>
<td>5.9</td>
</tr>
</tbody>
</table>

Abbreviations: NLR, negative likelihood ratio; PTP, pretest probability.

which patients required repeat ultrasonography for the possibility of a missed distal DVT on LCUS. In this latter study, the Wells’ criteria were simplified (Table 3) into a dichotomous outcome of pretest probability (“DVT likely” or “DVT unlikely”) [58,72]. Although other prediction rules exist, the modified Wells’ criteria are the most validated in the literature [36,55,73–75].

Studies by Wells and others can be assimilated into a simple clinical pathway to approach the diagnosis of DVT (Fig. 5) [36,55,65,74,76,77]. A negative D-dimer test or a negative LCUS in the “DVT unlikely” group rules out DVT and these patients do not require serial ultrasonography. All patients in the “DVT likely” group should undergo ultrasonography. In patients with a negative LCUS and positive D-dimer test, repeat ultrasonography is recommended to exclude the possibility of distal DVT, which have a 20% to 30% incidence of propagation [24].

When ultrasound is unavailable, other diagnostic modalities including CTV, magnetic resonance venography, and contrast venography may be used. Another approach is to administer one dose of low-molecular-weight heparin (LMWH) and arrange an outpatient ultrasound within 24 hours. Anderson and colleagues [74] validated the safety of this approach in low- and intermediate-risk patients. In this study, low-risk patients were given no treatment, whereas intermediate-risk patients were given one dose of LMWH before ED discharge. No patients developed PE or major bleeding within 48 hours of initial ED presentation.

Table 3
Clinical model for predicting the pretest probability of deep vein thrombosis

<table>
<thead>
<tr>
<th>Clinical characteristic</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Active cancer (treatment ongoing, administered within previous 6 mo or palliative)</td>
<td>1</td>
</tr>
<tr>
<td>Paralysis, paresis, or recent plaster immobilization of the lower extremities</td>
<td>1</td>
</tr>
<tr>
<td>Recently bedridden &gt; 3 d or major surgery within previous 12 wk requiring general or regional anesthesia</td>
<td>1</td>
</tr>
<tr>
<td>Localized tenderness along the distribution of the deep venous system</td>
<td>1</td>
</tr>
<tr>
<td>Swelling of the entire leg</td>
<td>1</td>
</tr>
<tr>
<td>Calf swelling &gt; 3 cm larger than asymptomatic side (measured 10 cm below tibial tuberosity)</td>
<td>1</td>
</tr>
<tr>
<td>Pitting edema confined to the symptomatic leg</td>
<td>1</td>
</tr>
<tr>
<td>Collateral superficial veins (nonvaricose)</td>
<td>1</td>
</tr>
<tr>
<td>Previously documented DVT</td>
<td>1</td>
</tr>
<tr>
<td>Alternative diagnosis at least as likely as DVT</td>
<td>−2</td>
</tr>
</tbody>
</table>

In patients who have symptoms in both legs, the more symptomatic leg is used. A score of 2 or higher indicates that the probability of DVT is “likely”; a score of less than 2 indicates that the probability is “unlikely.”

Abbreviation: DVT, deep venous thrombosis.

VTE occurs from an imbalance in endogenous fibrin formation and fibrinolysis. The cornerstone of VTE treatment is pharmacologic anticoagulation. Anticoagulants work by inhibiting the clotting cascade and shifting the imbalance back in favor of endogenous fibrinolysis. No randomized controlled trial has ever been performed proving the usefulness of heparin, and it was accepted as standard therapy before the widespread use of current diagnostic modalities. Treatment with either fixed-dosing LMWH or adjusted-dosing unfractionated heparin (UH) is acceptable. Benefits of LMWH include easier dosing, no required serial laboratory studies, and easier transition to the outpatient setting potentially decreasing hospital length of stay. A meta-analysis of LMWH versus UH found LMWH more efficacious with significantly less complications including major bleeding events and death, suggesting superiority of LMWH [78].

One major limitation of LMWH is cost. Two studies have now demonstrated that subcutaneous UH can be used alone to treat VTE with similar efficacy and safety as LMWH [79,80]. Furthermore, Kearon and colleagues [79] validated a safe and effective method of fixed-dosing subcutaneous UH that does not require following activated partial thromboplastin times. Pending further studies, subcutaneous UH may provide a significantly cheaper and promising alternative to LMWH.

Outpatient management of proximal DVT can be achieved with LMWH [81]. Although this is possible from the ED it requires a clinical pathway in

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**Fig. 5. Clinical algorithm for the diagnosis of suspected DVT. DVT, deep vein thrombosis; LCUS, limited compression ultrasonography.**
place that can ensure patient teaching, safety, and follow-up. Unfortunately, studies attempting to validate outpatient treatment from the ED suffer from such issues as prolonged ED stays and high patient exclusion rates [81,82].

Generalized fibrinolysis (commonly referred to as “thrombolysis”) is a less frequently used therapeutic intervention. Unlike heparin’s reliance on endogenous fibrinolysis, the administration of recombinant or bacterial tissue plasminogen activators increase circulating plasmin and accelerate fibrin breakdown. Although it has been shown to improve speed of clot resolution and a decreased incidence of postthrombotic complications [83], generalized fibrinolysis is associated with an increased risk of bleeding, including intracranial hemorrhage, and is generally not used in the management of DVT. Catheter-directed fibrinolysis and surgical thrombectomy are reserved for special situations including phlegmasia cerulea dolens and some cases of catheter-related upper-extremity DVT [26,84].

**Special cases**

Upper-extremity DVT includes thrombosis in the internal jugular, innominate, subclavian, or axillary veins. It occurs in approximately 16 per 100,000 persons in the United States [85]. Central access devices represent the largest risk factor and are associated with 80% of all upper-extremity DVTs [86]. Peripherally inserted central catheters, frequently used for their lower incidence of infectious complications, have a 10% to 40% incidence of upper-extremity DVT [87,88]. It is unclear why some patients form spontaneous (noncatheter associated) upper-extremity DVTs. An analysis of one large registry found younger age, lower body mass index, non-white race, and smoking to be factors more common in spontaneous upper-extremity DVTs, suggesting this entity has a different pathophysiology from other forms of VTE [89]. Although the incidences of PE and postthrombotic syndrome are poorly defined, upper-extremity DVTs warrant anticoagulation therapy [85,90].

Phlegmasia cerulea dolens is a severe form of DVT in which venous obstruction of the major deep veins and collateral veins leads to a sharp rise in venous pressure, massive interstitial fluid shifts, decreased arterial perfusion, compartment syndrome, and gangrene. Recognition of phlegmasia cerulea dolens (Fig. 6) is important in the ED for consideration of time-sensitive interventions, including anticoagulation, catheter-directed thrombolysis, and vascular surgical consultation [91–93].

Previously, it was believed that isolated calf DVTs did not pose a thromboembolic risk. Longitudinal studies have since shown a 20% to 30% incidence of clot propagation to the proximal venous system with a 20% incidence of embolization [94]. In symptomatic patients, LCUS provides only 73% sensitivity for distal DVTs [70]. High-risk patients with a negative LCUS and positive D-dimer test should undergo repeat ultrasound in 7 days to exclude propagation of a distal clot [56]. In addition to clot propagation
and PE, distal DVTs result in postthrombotic complications, such as pain, edema, and hyperpigmentation, in 10% to 38% of patients [24,94,95]. Treatment of distal DVT is controversial and either aspirin or low-dose LMWH therapy is currently acceptable. Given the incidence of clot propagation and postthrombotic complications, many clinicians recommend treating distal DVTs the same as proximal DVTs with full anticoagulation therapy [94]. When aspirin therapy is used alone, serial ultrasonography is recommended to ensure lack of propagation to proximal vessels.

Superficial thrombophlebitis in the absence of proximal DVT is not known directly to lead to PE. Approximately 8% of superficial thrombophlebitis can extend into the deep venous system, however, usually at the site of the proximal greater saphenous vein, and potentially embolize to the lung [96]. The main concern in the ED is to rule out superficial thrombophlebitis extension into the deep venous system by ultrasonography. Isolated superficial thrombophlebitis does not require admission, but treatment should be initiated to prevent propagation to deeper veins. Aspirin and LMWH both decrease superficial thrombophlebitis propagation and recurrence with similar efficacy and safety, and either is an acceptable option for superficial thrombophlebitis of the legs [97]. Graded compression stockings, heat pads, and elevation of the affected extremity may help provide symptomatic relief.

**Pulmonary embolism**

*Pathophysiology*

PE occurs when a thrombus breaks free from the endothelial wall, travels through the right side of the heart, and lodges into the narrowing pulmonary arteries. Depending on the size and shape of the clot, it may come to rest in the main pulmonary artery, in a tiny subsegmental artery, or...
anywhere in between. The shape may allow for normal blood flow or it may obstruct an entire vessel. Minute differences within the vasculature can lead to a myriad of pathophysiologic consequences resulting in a wide range of clinical signs and symptoms.

PE causes mismatching of ventilation and perfusion (V/Q). Alveoli with obstructed pulmonary capillaries become overventilated relative to the decreased blood flow, increasing functional dead space. Increased blood flow to unaffected pulmonary capillaries, despite unchanged alveolar ventilation, causes transpulmonary shunting. Pulmonary vascular resistance also increases by both the physical obstruction from the clot and inflammatory cytokine-mediated pulmonary vasoconstriction. The increase in pulmonary vascular resistance leads to increased right heart pressures, which can induce right heart failure or open previously closed atrial septal defects, leading to intracardiac shunting. In patients with normal lungs, the degree of pulmonary vascular resistance correlates with the degree of obstruction on pulmonary angiogram [98]. Pleural effusions develop from venous congestion and increased interstitial fluid secondary to ischemia and the release of inflammatory cytokines [99]. Pulmonary infarction is thought to be an uncommon occurrence from VTE because of the redundant oxygen sources including the pulmonary arteries, airways, and bronchial arteries. When thrombus obstructs smaller pulmonary arteries, blood can extravasate into alveoli preventing oxygenation from the airways. When this blood cannot be cleared quickly, as in left ventricular failure, pulmonary infarction can occur [98].

Clinical presentation

Symptoms associated with PE depend on the degree of vascular obstruction, the magnitude of inflammatory response, and the patient’s physiologic reserve. V/Q mismatch manifests as dyspnea, hypoxemia, and increased A-a gradient. Extravasation of blood into alveoli can cause pleuritic pain, cough, or hemoptysis. Increased pulmonary vascular resistance can lead to strain patterns on EKG; pleural effusions; right ventricular dilatation or hypokinesis; or severe right heart outflow obstruction manifesting as hypotension, syncope, or pulseless electrical activity cardiac arrest. It may also manifest as hypoxia if previously closed atrial septal defects open and cause significant transcardiac shunting. The natural history of PE is to present atypically and can include any combination of these findings or none at all.

Multiple studies have demonstrated the variability in clinical manifestations of PE (Table 4) [13,100]. The most common finding is dyspnea with 79% of patients with PE having dyspnea at rest or on exertion [13]. In PIOPED II, when PE was suspected and diagnosed, 97% to 98% of patients had at least one of the following: dyspnea, tachypnea, pleuritic pain, or signs of a DVT. Dyspnea or tachypnea was less frequent in elderly patients and at least one patient manifested circulatory collapse in the absence of dyspnea.
Table 4
Frequency of symptoms and signs in pulmonary embolus

<table>
<thead>
<tr>
<th>Symptoms of pulmonary embolism</th>
<th>No prior CPD</th>
<th>All patients</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>% PE</td>
<td>% No PE</td>
</tr>
<tr>
<td>Dyspnea</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dyspnea (rest or exertion)</td>
<td>73</td>
<td>68</td>
</tr>
<tr>
<td>Dyspnea (at rest)</td>
<td>55</td>
<td>46</td>
</tr>
<tr>
<td>Dyspnea (exertion only)</td>
<td>16</td>
<td>20</td>
</tr>
<tr>
<td>Orthopnea (&gt; 1-pillow)</td>
<td>28</td>
<td>24</td>
</tr>
<tr>
<td>Pleuritic chest pain</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chest pain (not pleuritic)</td>
<td>44</td>
<td>57a</td>
</tr>
<tr>
<td>Cough</td>
<td>19</td>
<td>22</td>
</tr>
<tr>
<td>Hemoptysis</td>
<td>34</td>
<td>28</td>
</tr>
<tr>
<td>Wheezing</td>
<td>5</td>
<td>3</td>
</tr>
<tr>
<td>Calf or thigh</td>
<td>21</td>
<td>18</td>
</tr>
<tr>
<td>Swelling</td>
<td>41</td>
<td>17b</td>
</tr>
<tr>
<td>Pain</td>
<td>44</td>
<td>23b</td>
</tr>
<tr>
<td>Calf and thigh</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Swelling</td>
<td>7</td>
<td>4</td>
</tr>
<tr>
<td>Pain</td>
<td>17</td>
<td>7b</td>
</tr>
<tr>
<td>Signs of pulmonary embolism</td>
<td>No prior CPD</td>
<td>All patients</td>
</tr>
<tr>
<td></td>
<td>% PE</td>
<td>% No PE</td>
</tr>
<tr>
<td>General</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tachypnea (≥ 20/min)</td>
<td>54</td>
<td>43a</td>
</tr>
<tr>
<td>Tachycardia (≥ 100/min)</td>
<td>24</td>
<td>14a</td>
</tr>
<tr>
<td>Diaphoresis</td>
<td>2</td>
<td>7a</td>
</tr>
<tr>
<td>Cyanosis</td>
<td>0</td>
<td>0.003</td>
</tr>
<tr>
<td>Temperature ≥38.5°C</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>(≥ 101.3°F)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardiac examination (abnormal)</td>
<td>21</td>
<td>11a</td>
</tr>
<tr>
<td>Increased P2</td>
<td>15</td>
<td>5b</td>
</tr>
<tr>
<td>Right ventricular lift</td>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td>Jugular venous distention</td>
<td>14</td>
<td>8%a</td>
</tr>
<tr>
<td>Lung examination (abnormal)</td>
<td>29</td>
<td>26</td>
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<tr>
<td>Rales (crackles)</td>
<td>18</td>
<td>14</td>
</tr>
<tr>
<td>Wheezes</td>
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<td>3</td>
</tr>
<tr>
<td>Rhonchi</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Decreased breath sounds</td>
<td>17</td>
<td>12</td>
</tr>
<tr>
<td>Pleural friction rub</td>
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<td>1</td>
</tr>
<tr>
<td>DVT signs</td>
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<td></td>
</tr>
<tr>
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<td>47</td>
<td>21b</td>
</tr>
<tr>
<td>Calf and thigh</td>
<td>14</td>
<td>4b</td>
</tr>
</tbody>
</table>

**Abbreviations:** CPD, cardiopulmonary disease; DVT, deep venous thrombosis; PE, pulmonary embolism; P2, pulmonary component of second sound.

a P < .05

b P < .01
c Edema, erythema, tenderness, or palpable cord.

Nondiagnostic tests

Similar to clinical signs and symptoms, most tests used in the ED have poor sensitivity and specificity for PE and are nondiagnostic. Nondiagnostic tests that may be abnormal in PE include electrocardiogram, chest radiograph, arterial blood gas, echocardiography, brain natriuretic peptide, and troponin-T. Nondiagnostic tests help suggest PE, but are inconclusive.

Electrocardiogram

The EKG occasionally reveals manifestations of right heart strain, usually in patients with massive PE. The most common finding in patients with non-massive PE is normal sinus rhythm. In patients with massive PE, anterior T-wave inversions were found more frequently (68%) than sinus tachycardia (28%) or S1Q3T3 (50%) (Fig. 7)[101]. The number of inverted T-waves in the anterior and inferior distribution seems to increase with severity of cor pulmonale and resulting subepicardial ischemia and predicts early complications from PE [102]. In a population of patients with confirmed PE studied by Kosuge and colleagues [103], T-wave inversions in both leads V1 and III had 99% specificity. Some authors suggest that the finding of simultaneous T-wave inversions in the anterior and inferior leads should prompt consideration of PE even when it had not been previously suspected.

Other EKG findings are less helpful. Sinus tachycardia is present in less than half of cases [13]. The classic S1Q3T3 pattern sometimes found in the subset of patients with right heart strain has low sensitivity and specificity. Atrial fibrillation, right bundle branch block, and axis change occur with considerable variability and are less clinically useful [104].

![Fig. 7. EKG findings in a patient with massive PE. Sinus tachycardia, S1Q3T3 (circles), and anterior-inferior T-wave inversions (triangles).](image-url)
Chest radiography

Manifestations of PE on chest radiograph include cardiomegaly, pleural effusions, elevated hemidiaphragm, pulmonary artery enlargement, atelectasis, infiltrate, pulmonary congestion, and the rarely described Hampton’s hump and Westermark’s sign. One study found that 76% of patients with PE have some abnormality on chest radiograph, but these abnormalities were nonspecific [105].

Arterial blood gas and pulse oximetry

The arterial blood gas and pulse oximetry do not reliably predict the presence of PE and 25% to 35% of patients with diagnosed PE have a normal arterial blood gas, pulse oximetry, and A-a gradient [106–108]. Obtaining arterial blood is relatively invasive and its inability to affect management makes it a less favored test among clinicians [108]. Furthermore, if fibrinolytics are being considered as a treatment option, arterial puncture should be limited.

Alveolar dead space measurements

When a PE obstructs blood flow to alveoli that are still ventilated, the amount of dead space is increased. An increase in dead space is indirect evidence of PE. Studies of alveolar dead space measurements combined with other clinical factors have shown promise in ruling out PE quickly and without imaging in the ED [109–111]. These measurements have not gained widespread acceptance in the ED because it requires obtaining an arterial blood gas and the presence of a respiratory therapist with specialized equipment to perform capnography.

Echocardiography

Echocardiography (echo) is a useful adjunct in the diagnosis of PE. Its application in the ED is most pertinent in patients presenting in extremis when rapid diagnosis is essential and fibrinolysis may be indicated. Furthermore, echo has the ability to rule out other conditions, such as pericardial effusion and tamponade, which also cause hypotension, but present a contraindication to fibrinolysis. Findings can include right ventricular dilatation (Fig. 8), right ventricular hypokinesis, intracardiac thrombus, abnormal septal wall motion, and loss of the normal inferior vena cava collapse index [112,113]. Grifoni and colleagues [113] demonstrated 51% sensitivity and 87% specificity of echo for PE, but when applied to patients with massive PE, sensitivity and NPV were 97% and 98%, respectively. Studies have demonstrated the ability of nonexpert sonographers to identify cardiac abnormalities associated with PE [114,115]. When echo is performed, ultrasound of the legs can easily be performed also to assess for DVT. Grifoni
and colleagues [113] also found that when two of three of the following clinical parameters were present (high clinical probability, right ventricular dilatation, or DVT) massive PE was present in 97% of patients with a NPV of 98%.

**Diagnostic tests**

Diagnostic tests are tests that maintain good clinical use in diagnosis of PE with either high sensitivity, specificity, or both. Diagnostic tests are often found in clinical algorithms and include D-dimer and various radiologic studies (CTA, CTV, CTA-CTV, V/Q scan, magnetic resonance angiography [MRA], pulmonary angiography).

**D-dimer**

The same principles apply to D-dimer in PE as in DVT. D-dimer tests have been combined with clinical prediction rules successfully and safely to reduce imaging. The use of the test depends on the likelihood ratio and acceptable posttest probability, which some claim less than 2% for PE. Generally, as in DVT, its use in PE is reserved for low probability patients, because it is only in this group that a negative D-dimer test acceptably rules out PE. There are multiple types of D-dimer and one must be familiar with the operating characteristics, specifically the NLR, of the D-dimer test in one’s own institution.

**CT**

CTA has become the imaging test of choice to diagnose PE [116]. It is quick, widely available, relatively noninvasive, and performs similarly to...
formal pulmonary MRA [117]. Studies of multidetector row CTA (MDR-CTA) show an 82% to 100% sensitivity and 89% to 98% specificity for diagnosing PE [117–120]. CTA provides a diagnostic binary outcome (“PE” or “no PE”) in 95% of cases, making it preferred over other imaging modalities, such as V/Q scan, which may provide indeterminate results [121]. Furthermore, CTA often offers alternative diagnoses when PE is absent.

Data from PIOPED II shows that CTA follows the rules of Bayes’ theorem similarly to other diagnostic tests in VTE, in that the positive and negative predictive values of CTA are affected by the pretest probability of disease. A negative CTA is more likely a true-negative in the low-risk group, and a positive CTA is most likely a true-positive in the high-risk group (Table 5) [118]. In high-risk patients, the NPV is a disappointing 60%. In this group, the addition of CTV to CTA augments the NPV to 82% and is recommended [116,122–124].

The weakness of CTA is its poor ability to detect small peripheral PEs. Despite improved visualization of segmental and subsegmental PEs with MDR-CTA over single-detector row CTA, these emboli are still imaged poorly with CT [117,120,125]. In addition, MDR-CTA often overrepresents subsegmental PEs when they are not present. In PIOPED II, a subsegmental PE in a low clinical probability patient was most often a false-positive with a positive predictive value of only 25% [118]. Furthermore, there is poor interobserver agreement between radiologists when diagnosing subsegmental PE on CT scan [120,125].

The dilemma in diagnosing smaller peripheral PEs is underscored by the uncertainty of their clinical significance. Studies comparing MDR-CTA with single-detector row CTA show a higher diagnosis rate of subsegmental PEs with MDR-CTA [120,126]. Some argue that these subsegmental emboli are significant, because MDR-CTA does not increase the overall diagnosis rate of PE when compared with previous studies, such as PIOPED I.

<table>
<thead>
<tr>
<th>Table 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive predictive values and negative predictive values of computed tomographic angiography and venography compared with previous clinical assessment</td>
</tr>
<tr>
<td>Clinical probability</td>
</tr>
<tr>
<td>Clinical probability</td>
</tr>
<tr>
<td>PPV CTA</td>
</tr>
<tr>
<td>PPV CTA or CTV</td>
</tr>
</tbody>
</table>

**Abbreviations:** CTA, computed tomographic angiography; CTV, computed tomographic venography; NPV, negative predictive value; PPV, positive predictive value.

suggesting these subsegmental PEs were also picked up on V/Q scan and pulmonary angiography [12]. A recent randomized controlled trial of MDR-CTA versus V/Q scan, however, proves otherwise. In this study MDR-CTA increased the diagnosis rate of PE (19%) compared with V/Q scan (14.2%) [127]. In patients in whom PE was excluded, 0.4% of the MDR-CTA group and 1% of the V/Q scan group developed VTE in follow-up. Despite the superior detection of PE with MDR-CTA, withholding anticoagulation based on a negative single-detector row CTA scan seems to be safe with less than 1% of patients developing VTE after 3 months [128,129]. These findings prompt the question whether these additional subsegmental PEs found on MDR-CTA are clinically relevant. No study has demonstrated safety in withholding anticoagulation to patients with diagnosed isolated subsegmental PEs, but some authors liken them to distal DVTs that do not necessarily warrant full anticoagulation. Given the dynamic balance of fibrin formation and breakdown in the body, some believe that one of the natural functions of the lung vasculature is to filter the blood and prevent clots from traveling to other end-organs. Others believe, however, that diagnosis of subsegmental PE is evidence of a prothrombotic state and increased risk for further VTE.

Drawbacks to CTA are mainly radiation exposure and possible untoward effects of intravenous contrast including anaphylactoid reactions, contrast extravasation, and contrast nephropathy. Additionally, renal insufficiency, prior contrast allergy, and hemodynamic instability are relative contraindications, or require preparation.

Ventilation-perfusion scanning

Before single and MDR-CT, the V/Q scan was the first-line imaging modality for PE. It is a nuclear imaging test that assesses for areas of ventilation without perfusion as evidence of PE. Scan results include normal, low probability, intermediate probability, or high probability. The appropriate interpretation of results depends on assessment of pretest probability. In the original PIOPED study, a high probability scan was 96% accurate when the clinical probability was high, but only 56% accurate when clinical probability was low [12]. Furthermore, 57% of patients with PE had low- or intermediate-probability V/Q scans. Because of frequent indeterminate results, V/Q scans do not affect management 40% to 60% of the time, making it a less popular test in the ED [130].

Patients who have structurally abnormal lungs from chronic lung disease, mass, cavitation or other pathology usually have an abnormal V/Q scan despite the absence of PE. A normal chest radiograph increases the likelihood of a diagnostic V/Q scan, whereas patients with abnormal chest radiographs have diagnostic scintigraphy only 9% of the time in one report [131]. Still, the V/Q scan is useful and needed in a subset of patients with a contraindication to CT. Data from PIOPED II are more promising for V/Q scan than
PIOPED I, finding a determinate result of “PE” or “no PE” in 77.4% of patients [121].

**Pulmonary angiography**

Pulmonary angiography is the gold standard for PE diagnosis, but its many disadvantages make it less useful in the ED. It is invasive, expensive, and generally not readily available. Furthermore, CTA now provides a modality with near identical detection rates. In a comparison of digital subtraction pulmonary angiography with MDR-CTA, MDR-CTA demonstrated 100% sensitivity and specificity of 89% with digital subtraction pulmonary angiography as the reference standard. More proximal clots were detected with MDR-CTA, whereas digital subtraction pulmonary angiography picked up more distal clots. There were three false-positives on MDR-CTA, which when reviewed had characteristic appearances of PE. Even though they were not seen on digital subtraction pulmonary angiography, the authors suggested that these were probably true-positives and the digital subtraction pulmonary angiography was incorrect. If MDR-CTA was used as the reference standard, pulmonary angiography would have a sensitivity, specificity, and accuracy of 86%, 100%, and 97%, respectively [117].

**Magnetic resonance angiography**

MRA provides another diagnostic choice in PE diagnosis. Multiple MRA techniques exist with varying degrees of accuracy. The most common is gadolinium-enhanced MRA, which accurately identifies proximal clots, but poorly detects subsegmental emboli. Oudkerk and colleagues [132] found a sensitivity of 77% and specificity of 98% of gadolinium-enhanced MRA for PE. Real-time MRI improves on gadolinium-enhanced MRA by timing MRI scanning with patient breathing. Its sensitivity and specificity was 85% and 98% in a study by Kluge and colleagues [133]. Neither gadolinium-enhanced MRA nor real-time MRI achieves sensitivity to function as a single diagnostic test. Recently, MR perfusion scanning was developed, which uses signals from gadolinium to estimate blood volume in regions of the lung. Identification of decreased blood volume represents indirect evidence of PE. Although studies are few, one study found a sensitivity and specificity of 100% and 91%, respectively, when perfusion MRI was compared with MDR-CTA [133].

Advantages of MRA include elimination of ionizing radiation, safety in pregnancy, and decreased nephrotoxicity from contrast enhancing agents. Still, failure to demonstrate adequate sensitivity, costs, and lack of availability makes this modality not a standardized test in diagnosing PE. Many studies are underway including one by PIOPED investigators comparing MRA with CT, which will further define the role of MRA in VTE diagnosis.
Clinical pathway

As with DVT, optimal work-up of PE begins with an assessment of pre-test probability. Multiple scoring systems exist to aid clinicians, but perform no better than experienced clinical judgment [134]. The most studied and accessible scoring systems are the simplified Well’s criteria and revised Geneva score (Table 6). Objective scoring systems have the advantage of being able successfully to stratify patients into appropriate risk categories even with little physician experience [135].

Because PE presents atypically, it should be considered often in the ED. Overuse of D-dimer testing is problematic, however, leading to overtesting and more false-positives. To avoid this problem, Kline and colleagues [136] developed the pulmonary embolus rule out criteria rule to identify which low-risk patients do not need D-dimer or other testing, essentially a close to no-risk group (Box 2). When all eight pulmonary embolus rule out

<table>
<thead>
<tr>
<th>Revised Geneva score</th>
<th>Points</th>
<th>Simplified Wells’ score</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age &gt;65 y</td>
<td>1</td>
<td>Clinical signs or symptoms of DVT (leg swelling and pain with palpation of deep veins of leg)</td>
<td>3</td>
</tr>
<tr>
<td>Previous DVT or PE</td>
<td>3</td>
<td>No alternate diagnosis as likely or more likely than PE</td>
<td>3</td>
</tr>
<tr>
<td>Surgery (under general anesthesia) or fracture (of the lower limbs) within 1 mo</td>
<td>2</td>
<td>Heart rate &gt;100 beats per min</td>
<td>1.5</td>
</tr>
<tr>
<td>Active malignant condition (solid or hematologic malignant condition, currently active or considered cured &lt;1 y)</td>
<td>2</td>
<td>Immobilization or surgery in last 4 wk</td>
<td>1.5</td>
</tr>
<tr>
<td>Unilateral lower-limb pain</td>
<td>3</td>
<td>Previous history of DVT or PE</td>
<td>1.5</td>
</tr>
<tr>
<td>Hemoptysis</td>
<td>2</td>
<td>Hemoptysis</td>
<td>1</td>
</tr>
<tr>
<td>Heart rate</td>
<td></td>
<td>Cancer actively treated in last 6 mo</td>
<td>1</td>
</tr>
<tr>
<td>75–94</td>
<td>3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥95</td>
<td>4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pain on lower-limb deep venous palpation and unilateral edema</td>
<td>4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clinical probability</td>
<td>Low</td>
<td>Clinical probability</td>
<td></td>
</tr>
<tr>
<td></td>
<td>0–3</td>
<td>Low</td>
<td>0–1</td>
</tr>
<tr>
<td></td>
<td>Intermediate</td>
<td>4–10</td>
<td>2–6</td>
</tr>
<tr>
<td></td>
<td>High</td>
<td>≥11</td>
<td>≥7</td>
</tr>
</tbody>
</table>

**Abbreviations:** DVT, deep venous thrombosis, PE, pulmonary embolism.

When testing is needed, clinical judgment or clinical prediction rules, such as the simplified Wells’ or revised Geneva score, should be implemented to stratify patients into risk categories.

Low-probability patients should undergo testing with a rapid ELISA or an equivalent highly sensitive D-dimer test. A positive result prompts further testing, generally with CTA (Fig. 9). There is some debate to the use of D-dimer in the intermediate probability group. Although some studies have demonstrated that a single D-dimer may safely be used in the intermediate-risk group, the clinician must be aware that the posttest probability from a negative D-dimer in this group was still 5% (assuming a pretest probability of 30% and a NLR of 0.1) [62,118]. The use of D-dimer testing in the intermediate-risk group should depend on the NLR of the D-dimer test and the comfort of the EP. Intermediate-risk patients with a positive D-dimer test should undergo CTA. High-risk patients should undergo CTA-CTV because the addition of CTV to CTA increases the NPV from 60% to 82% in this group [118].

### Treatment and management

On diagnosis or high suspicion of PE, rapid initiation of therapy can be lifesaving. Treatment with either UH or LMWH is acceptable and the principles are similar to treatment of DVT.

When PE is strongly suspected (ie, high probability), initiation of heparin therapy before radiologic confirmation likely provides more benefit than risk. Clots can enlarge at an exponential rate. Furthermore, normotensive patients who die from PE do so within the first 24 hours, underscoring

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**Box 2. Pulmonary embolism rule out criteria rule**

- Age <50
- Pulse <100
- Oxygen saturation >94%
- No unilateral leg swelling
- No hemoptysis
- No recent surgery or trauma
- No prior PE or DVT
- No hormone use

If all present <2% risk of PE in low-risk groups.

the importance of rapid assessment and treatment. In patients with PE and an absolute contraindication to anticoagulation or patients already on full anticoagulation, an emergent inferior vena cava filter should be considered.

Fibrinolytics rapidly dissolve clot by active breakdown of fibrin, but they are nonselective and can cause severe bleeding. Fibrinolysis involves the administration of recombinant or bacterial tissue plasminogen activators that increase circulating plasmin and accelerate fibrin breakdown. Their use is generally recommended for massive PE with hemodynamic instability where the risk of bleeding is overshadowed by the potential benefits, but the benefit is unclear. Multiple case reports and small case series suggest potential improved outcomes and return of spontaneous circulation following fibrinolytic administration [137–140]. In a study by Kucher and colleagues [141], fibrinolytic therapy did not decrease 90-day mortality or recurrence of PE in patients with massive PE. The data are equally as unimpressive in patients with submassive PE [142,143]. Still, fibrinolysis should be considered in patients who show signs of clinical deterioration with worsening respiratory distress or hypotension because PE-related cardiac arrest has a dismal prognosis.

Fig. 9. Clinical algorithm for the diagnosis of suspected PE. CTA, computed tomography angiography; CTV, computed tomography venography; MRV, magnetic resonance venography; NLR, negative likelihood ratio; NPV, negative predictive value; PERC, pulmonary embolus rule-out criteria; PPV, positive predictive value; PTP, pretest probability. *Prevalence rates of PE for each pretest probability group based on multiple clinical prediction rules (Empiric, Wells’ Extended, Wells’ Simplified, Geneva, Geneva Revised) from PIOPED II. Calculations assume D-dimer with NLR of 0.1. $\subseteq$ Low PTP CTA: main or primary lobar PE PPV 97%, segmental PPV 68%, subsegmental PPV 25%. (Adapted from Stein PD, Woodard PK, Weg JG, et al. Diagnostic pathways in acute pulmonary embolism: recommendations of the PIOPED II investigators [see comment]. Am J Med 2006;119:1048–55; with permission.)
In patients with massive PE refractory to fibrinolysis, surgical embolec-
tomy performs better than repeat fibrinolysis [144]. Embolectomy provides
a reasonable and potentially lifesaving final therapeutic pathway in massive
PE. When successful, patients have excellent long-term results [145].

In addition to selection of appropriate therapies, the EP must also deter-
mine appropriate triage of patients with PE. Patients with massive PE
deserve ICU level care because they have the poorest prognosis. Normoten-
sive patients with submassive PE and cor pulmonale evidenced by anterior
and inferior T-wave inversions on EKG, elevated brain natriuretic peptide,
elevate troponin-T, or right heart dilatation or hypokinesis on echocardiogra-
phy have poorer clinical outcomes and may benefit from a higher level of
care [102,146–148]. Normotensive patients without right heart strain generally
have excellent clinical outcomes [148] and can likely be admitted to
hospital ward beds.

Considerations for special populations

Pregnancy

VTE is the most frequent cause of death in pregnancy with the highest
risk in the postpartum period [149,150]. As with nonpregnant patients,
symptoms and signs of VTE can be highly variable. Because many trials ex-
clude pregnant patients, questions arise as to the correct usage of diagnostic
testing in this population.

Use of D-dimer testing in pregnancy is controversial. As in nonpregnant
patients, D-dimer tests provide good sensitivity, but specificity decreases as
gestational age increases [151]. Lower specificity means D-dimer tests increase
the number of negative diagnostic VTE tests. When signs of DVT are present,
ultrasound is the recommended diagnostic strategy because it poses no known
risk to the fetus. When PE is suspected, presence of DVT clinches the diagno-
sis, but when symptoms of DVT are absent, ultrasound is rarely positive [152].

Previously, V/Q scan was recommended over CTA as the initial diagnos-
tic study for PE in pregnant patients because of decreased radiation expo-
sure. Newer-age CT scanners have significantly less radiation delivered to
the fetus to near equal or even lower doses of radiation from V/Q scanning
[153]. Because V/Q scanning frequently produces indeterminate results,
CTA is preferred. MRA or venography may be promising for VTE diagno-
sis in pregnancy, but clinical studies have yet to be performed in this popu-
lation precluding its recommendation at this time. Treatment of VTE in
pregnancy is the same as VTE in other populations with the exception
that warfarin, a known teratogen, cannot be used.

Comorbid conditions

Various comorbid conditions, such as congestive heart failure and chronic
obstructive pulmonary disease, may commonly present with symptoms
similar to VTE. When VTE is present in these patients, it is often not recognized. This is worsened by the fact that debilitating conditions place patients at increased risk for PE from immobility and sedentary lifestyle and are often associated with other risk factors, such as obesity and smoking.

Autopsy studies suggest that patients with chronic obstructive pulmonary disease have a high rate of missed PE [154]. Two prospective studies evaluated all patients presenting with chronic obstructive pulmonary disease exacerbations for PE and found very different prevalence rates. Tillie-Leblond and colleagues [155] found a prevalence of 25% of PE (49 of 197), whereas Rutschmann and colleagues [155,156] found a prevalence rate of only 3.3% (4 of 123). The explanation for the difference in prevalence rates is unclear. Further studies need to clarify the prevalence of PE in this population. Still, a high index of suspicion in patients with chronic obstructive pulmonary disease, congestive heart failure, and other comorbid conditions that may mask symptoms of PE is appropriate, particularly because of the worse outcomes associated with these patients.

Summary

The approach to VTE in the ED has evolved tremendously over the last 20 years. Pretest probability scores and clinical pathways using highly sensitive rapid D-dimer tests have been established and validated. This has safely reduced costly and invasive radiographic evaluation, improving the diagnosis of DVT and PE. Furthermore, EP-performed ultrasound is now a well-established, fast, and accurate method of ruling out DVT. The advent of MDR-CTA has increased the detection rate of PE, but recent data have revealed that, like V/Q scans, predictive values of CTA depend on pretest probability. Treatment of VTE with intravenous UH or subcutaneous LMWH is well-established, with the latter preferred because of ease of administration and lower rates of adverse events. Subcutaneous UH may play a future role, however, as sole treatment of VTE. Fibrinolysis has had disappointing results and its appropriate role in VTE is yet to be determined. Use of fibrinolysis should be limited to patients with massive PE in cardiopulmonary extremis until further clinical trials are performed. Many issues still exist including underdiagnosis in some patients and concerns of possible overdiagnosis in others. It is unclear whether all patients with proximal DVT or subsegmental PE benefit from anticoagulation, and perhaps future studies will elucidate this further. Current studies are under way to research other modalities, such as MRA, to diagnose PE better.

Acknowledgment

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References


