Clinical Policy: Critical Issues in the Evaluation and Management of Adult Patients Presenting With Suspected Pulmonary Embolism

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This clinical policy was developed by the ACEP Clinical Policies Committee and the Clinical Policies Subcommittee on Suspected Pulmonary Embolism. For a complete listing of subcommittee and committee members, please see p. 266.

This clinical policy focuses on critical issues in the evaluation and management of patients with signs or symptoms of pulmonary embolism (PE). A MEDLINE search for clinical trials published from January 1995 through April 2001 was performed using the key words "pulmonary embolus" with limits of "clinical investigations" and "clinical policies." Subcommittee members and expert peer reviewers also supplied articles with direct bearing on the policy. This policy focuses on 2 major areas of current interest and/or controversy: (1) diagnostic: utility of D-dimer, ventilation-perfusion scanning, and spiral computed tomography angiogram in the evaluation of PE; and (2) therapeutic: indications for fibrinolytic therapy. Recommendations for patient management are provided for each 1 of these topics based on strength of evidence (Level A, B, or C). ***Level A recommendations*** represent patient management principles that reflect a high degree of clinical certainty; ***Level B recommendations*** represent patient management principles that reflect moderate clinical certainty; and ***Level C recommendations*** represent other patient management strategies based on preliminary, inconclusive, or conflicting evidence, or based on panel consensus. This guideline is intended for physicians working in emergency departments or chest pain evaluation units.

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INTRODUCTION

Approximately 600,000 patients each year are diagnosed with pulmonary embolism (PE).[1] Untreated PE can be rapidly fatal,[2] and some survivors of undiagnosed PE can suffer disabling morbidity from pulmonary hypertension.[3] Because there is a strong association between deep venous thrombosis (DVT) and PE, it is difficult to discuss the diagnostic evaluation of one entity without discussing the other.[4] Approximately 50% of patients with documented DVT have perfusion defects on nuclear lung scanning, and asymptomatic venous thrombosis is found in approximately 40% of patients with confirmed PE.[1,5,6] The American College of Emergency Physicians (ACEP) will discuss critical issues in the evaluation of DVT in a separate policy.

Over the past decade, there has been an explosion of published research and development of new diagnostic modalities and therapies relating to patients with suspected PE and DVT, with greater than 1,000 publications appearing in the medical literature per year. The 1995 ACEP "Clinical Policy for the Initial Approach to Adults Presenting with a Chief Complaint of Chest Pain, With No History of Trauma," addressed PE in presenting signs and symptoms, predisposing risk factors, diagnosis, treatment, and subsequent disposition.[7] In 1999, a decision was made to develop a revised chest pain policy that focused initially on critical issues in evaluation and management of patients with suspected acute myocardial infarction (AMI) or unstable angina to be followed by a policy focusing on patients with suspected PE. The AMI/unstable angina policy was published in May 2000.[8] This current policy represents a revision of the 1995 chest pain clinical policy as it relates to the initial approach to patients with signs and symptoms of PE. Future clinical policies may address other significant causes of chest pain that were the focus of the 1995 clinical policy. It is hoped that departure from the previous format will improve patient care and direct critical areas of future research.

Recommendations offered in this policy are not intended to represent the only diagnostic and management options that the emergency physician should consider. ACEP clearly recognizes the importance of the individual clinician's judgment. Rather, they define for the clinician those strategies for which medical literature exists to provide strong support for their utility in answering the crucial questions addressed in this policy.

METHODOLOGY

This clinical policy was created after careful review and critical analysis of the peer-reviewed literature. All papers were graded by at least 2 subcommittee members for strength of evidence. An initial MEDLINE search for articles published from January 1995 through April 2001 was performed using the key words "pulmonary embolus" and yielded 5,004 hits. The search was therefore limited to clinical trials and clinical policies, which reduced the hits to 356. The abstracts from these articles were reviewed by subcommittee members who then met to select areas of critical importance on which to focus this policy. Pertinent practice guidelines reviewed in the development of this document included the 1996 American Heart Association "Management of Deep Vein Thrombosis and Pulmonary Embolism,"[1] the 1997 British Thoracic Society "Suspect Acute Pulmonary Embolism: A Practical Approach,"[9] the 1998 American College of Chest Physicians consensus statement "Opinions Regarding the Diagnosis and Management of Venous Thromboembolic Disease,"[10] the 1999 American Thoracic Society "The Diagnostic Approach to Acute Venous Thromboembolism,"[11] and the 2000 European Heart Society "Diagnosis and Management of Acute Pulmonary Embolism."[12] Subcommittee members also supplied references with direct bearing on the policy by reviewing bibliographies of initially selected papers or from their own knowledge base. After review of the initial literature, the committee determined that emphasis should be placed on the following topics: (1) diagnostic: utility of D-dimer, ventilation-perfusion (V/Q) lung scan, and spiral computed tomography (CT) angiogram in the evaluation of PE; and (2) therapeutic: indications for fibrinolytic therapy in PE.

This policy is not intended to be a complete manual on the initial evaluation and management of patients

with suspected PE but rather a focused look at critical issues that have particular relevance to the practice of emergency medicine. Detailed treatises on risk factors, etiology, pathophysiology, physical examination findings, and anticoagulation therapy can be found in any standard textbook of emergency medicine or internal medicine. Some areas considered for discussion but not included in this policy (and therefore not graded) were use of low-molecular-weight heparin,[13-15] newer treatment modalities,[16] effectiveness of aspirin in PE prophylaxis,[17] indications for vena cava filter placement,[18] risk factors for predicting recurrence,[19] magnetic resonance imaging angiography,[20-25] transthoracic and transesophageal echocardiography,[26-33] and alveolar deadspace calculation.[34] These areas represent topics that ACEP may address in future updates of this current policy.

The reasons for developing clinical policies in emergency medicine and the approaches used in their development have been enumerated.[35] This policy is a product of the ACEP clinical policy development process, including expert review, and is based on the existing literature; where literature was not available, consensus of emergency physicians was used. Expert review comments were received from individual emergency physicians; physicians from other specialties, such as cardiologists; and specialty societies, including members of the American College of Cardiology, American College of Chest Physicians, American College of Radiology, American Lung Association, and the Society of Thoracic Radiology. Their responses were used to further refine and enhance this policy. Clinical policies are scheduled for revision every 3 years; however, interim reviews are conducted when technology or the practice environment changes significantly.

During the review process, all papers used in the formulation of this policy were classified by the subcommittee members into 3 classes based on design of study, with design 1 representing strongest evidence and design 3 representing weakest evidence for therapeutic, diagnostic, and prognostic clinical reports respectively (Appendix A). Reports were then graded on 6 dimensions thought to be most relevant to the development of a clinical guideline: blinded versus nonblinded outcome assessment, blinded or randomized allocation, direct or indirect outcome measures, biases (eg, selection, detection, transfer), external validity (generalizability), and sufficient sample size.[36-38] Articles received a final grade (I, II, III) based on a predetermined formula taking into account design and grade of study (Appendix B). Articles with fatal flaws were given an "X" grade and not used in the creation of this policy.

Clinical findings and strength of recommendations regarding patient management were then made according to the following criteria:

Level A recommendations. Generally accepted principles for patient management that reflect a high degree of clinical certainty (ie, based on "strength of evidence class I" or overwhelming evidence from "strength of evidence class II" studies that directly address all the issues).

Level B recommendations. Recommendations for patient management that may identify a particular strategy or range of management strategies that reflect moderate clinical certainty (ie, based on "strength of evidence class II" studies that directly address the issue, decision analysis that directly addresses the issue, or strong consensus of "strength of evidence class III" studies).

Level C recommendations. Other strategies for patient management based on preliminary, inconclusive, or conflicting evidence or, in the absence of any published literature, based on panel consensus.

There are certain circumstances in which the recommendations stemming from a body of evidence should not be rated as highly as the individual studies on which they are based. Factors such as heterogeneity of results, uncertainty about effect magnitude and consequences, strength of prior beliefs and publication bias, among others, might lead to such a downgrading of recommendations.

Scope of application. This guideline is intended for physicians working in emergency departments or chest pain center evaluation units.

Inclusion criteria. This guideline is intended to apply to adult patients presenting with signs or symptoms of PE.

Exclusion criteria. Pregnant patients and asymptomatic patients.

CRITICAL ISSUES IN PULMONARY EMBOLISM

Estimation of pretest probability of the disease is imperative for proper application of results of diagnostic testing. The pretest probability of PE can be estimated by using explicit criteria that are available in virtually every ED. Multiple methods have been examined, but the 3 methods that appear to be most applicable to ED patients are the Wells et al[39-41] criteria derived from a thromboembolism referral center in Canada, the Wicki et al[42] criteria derived from a single hospital in Switzerland, and the Kline et al[43] criteria derived from 7 urban EDs in the United States. The Wells et al and Wicki et al scoring system assign a number to certain specific findings in patients with suspected PE (Table 1 and 2). The numbers are added up to generate a score, which corresponds to a pretest probability for PE. With either system, low-risk patients (40% to 49% of total patients) had less than a 10% probability of PE, and high-risk patients (6% to 7% of total patients) had greater than 65% probability of PE. Intermediate-risk patients comprised approximately half of the patients with a probability of PE in the 20% to 40% range. Sanson et al[44] performed a multicenter trial comparing subjective physician judgement of pretest probability for PE to the extended Wells et al[39] model and the simplified Wells et al[40,41] model. In this study, the rates of PE in the low-risk groups were 19% for subjective physician judgement, 28% for the extended Wells et al model, and 28% in the simplified Wells et al[44] model. The 3 methods yielded comparative predictive values in patients with intermediate and high risk for PE. These findings emphasize the need for ongoing prospective studies to validate and improve structured models for predicting risk of PE.[45] The Kline et al[43] scoring system was developed to identify patients who were safe for use of D-dimer testing for exclusion of PE (Figure). In this study, 934 patients with suspected PE were prospectively inter-

Table 1.
Wells et al[41] criteria for assessment of pretest probability for PE.

Criteria	Points
Suspected DVT	3.0
An alternative diagnosis is less likely than PE	3.0
Heart rate >100 beats/min	1.5
Immobilization or surgery in the previous 4 wk	1.5
Previous DVT/PE	1.5
Hemoptysis	1.0
Malignancy (on treatment, treated in the past 6 mo or palliative)	1.0

Score Range	Mean Probability of PE, %	% With This Score	Interpretation of Risk
<2 points	3.6	40	Low
2–6 points	20.5	53	Moderate
>6 points	66.7	7	High

Reprinted with permission from Wells PS, Anderson DR, Rodger M, et al. Derivation of a simple clinical model to categorize patient's probability of pulmonary embolism: increasing the models utility with the SimpliRED D-dimer. *Thromb Haemost.* 2000;83:416-420.

Table 2.
Wicki et al[42] criteria for assessment of pretest probability for PE.

Criteria	Points
Age 60–79, y	1
Age >79, y	2
Prior DVT/PE	2
Recent surgery	3
Heart rate >100 beats/min	1
$Paco_2$, mm Hg	
<36	2
36–39	1
Pao_2, mm Hg	
<49	4
49–60	3
>60–71	2
>71–82	1
Chest x-ray	
Plate-like atelectasis	1
Elevation of hemidiaphragm	1

Score Range	Mean Probability of PE, %	% With This Score	Interpretation of Risk
0–4	10	49	Low
5–8	38	44	Moderate
9–12	81	6	High

Reprinted with permission from Wicki J, Perneger T, Junod A, et al. Assessing clinical probability of pulmonary embolism in the emergency ward: a simple score. *Arch Intern Med.* 2001;161:92-97. Copyrighted 2001, American Medical Association.

viewed and examined for recognized signs, symptoms, and risk factors for PE. Unsafe patients were defined as patients whose pretest probability for PE was sufficiently high (>40%) that a negative quantitative D-dimer (–LR 0.07) could not reliably exclude the diagnosis. After multivariate logistic regression of 14 independent clinical variables, unsafe patients for D-dimer testing were defined as patients with a shock index (heart rate/systolic blood pressure) greater than 1.0 or age greater than 50 years, together with any one of the following conditions: unexplained hypoxemia (Sao_2 <95%; no prior lung disease), unilateral leg swelling, recent major surgery, or hemoptysis. Incidence of PE was 42.1% in unsafe patients (high risk) and 13.3% in safe patients (low risk).[43] Prospective validation of the Kline et al scoring system has yet to be performed.

The criterion standard for diagnosis or exclusion of PE remains the bilateral pulmonary angiogram.[1,9-12] The pulmonary angiogram has many drawbacks as a primary screening test for PE, in terms of high cost, time to perform, and test availability. Although the Prospective Investigation of Pulmonary Embolism Diagnosis (PIOPED) study[46] found that intra-observer agreement for the pulmonary angiogram was 98% for lobar PE, 90% for segmental PE, and 66% for subsegmental PE, the diagnostic accuracy of the pulmonary angiogram in the community hospital setting is currently unknown. Also, the significance of subsegmental PE is unclear, especially in light of the poor intra-observer agreement in the PIOPED study.[46-49] As a result, many investigators have suggested a shift to patient outcome (eg, recurrent PE, death) as the criterion standard as opposed to the pulmonary angiogram.[47-49] Currently, the pulmonary angiogram is usually reserved for difficult cases where other screening tests have yielded indeterminant or conflicting information.

CRITICAL QUESTIONS

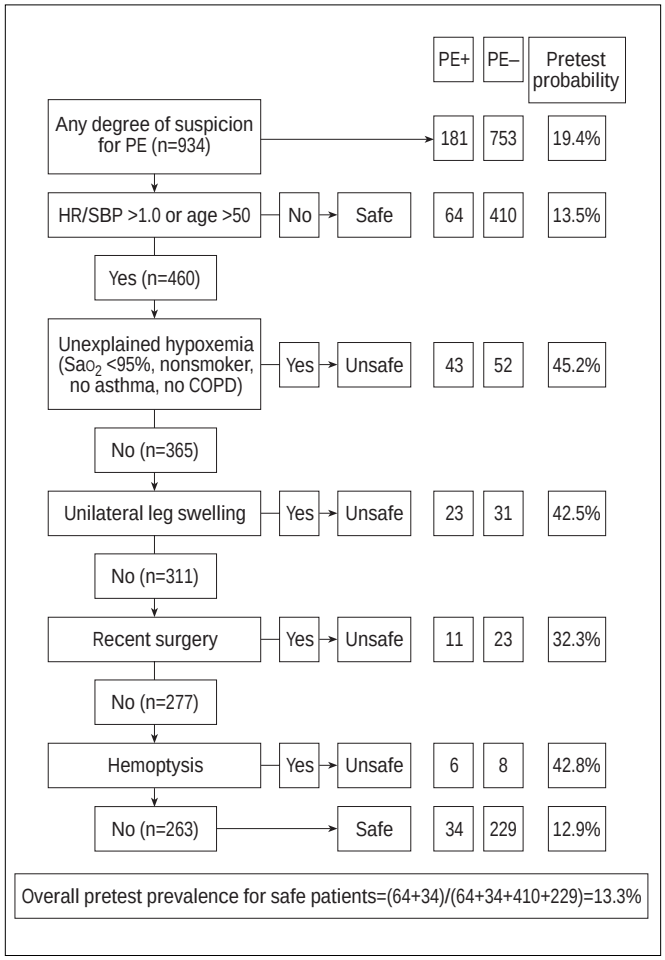
I. Can a negative D-dimer exclude PE?

D-dimers are released as a result of fibrinolysis, and thus serve as a circulating marker of the presence of

Figure.

Kline et al[43] decision rule for excluding PE. Reprinted with permission from Kline JA, Nelson RD, Jackson RE, et al. Criteria for the safe use of D-dimer testing in emergency department patients with suspected pulmonary embolism: a multicenter US study. Ann Emerg Med. *2002;39:144-152.*

Flow diagram demonstrating how the decision rule works to determine whether a patient can have PE ruled out with either a negative D-dimer plus alveolar deadspace measurement or a quantitative D-dimer assay of <500 ng/mL (either procedure hereafter referred to as D-dimer testing). First, any ED patient with any degree of suspicion for PE can be considered. Next, if the patient is ≤50 years of age and the heart rate is less than or equal to the systolic blood pressure (ie, shock index ≤1.0), the patient is immediately eligible for D-dimer testing. If the patient is either >50 years or has a shock index of >1.0, the clinician should ask 4 sequential questions: (1) Does the patient have unexplained hypoxemia? (2) Does the patient have unilateral leg swelling? (3) Has the patient had surgery requiring general anesthesia in the past 4 weeks? (4) Does the patient have hemoptysis? If the answer to all 4 questions is "no," then the patient is still eligible for D-dimer testing. This decision rule splits the patients into 2 groups: four fifths of whom are eligible for D-dimer testing ("safe" patients with pretest probability of PE of 13.3%) and one fifth of whom are ineligible for D-dimer testing ("unsafe" patients with pretest probability of 42.1%).



endovascular thrombus. To use D-dimer testing to exclude the diagnosis of PE, one must make a pretest probability assessment as discussed previously. Pretest probability for PE can be performed using 1 of the various scoring systems (pretest probability 3.6% to 13.3%)[39,40,43] or by subjective physician judgment (pretest probability 19%).[44] Based on theoretical analysis, if a patient has a pretest probability for PE of less than 20%, a D-dimer assay with a –LR of 0.08 lowers the posttest probability to less than 2% and a D-dimer assay with a –LR of 0.04 lowers the posttest probability to less than 1%. Likewise, if a patient has a pretest probability for PE of less than 10%, a D-dimer assay with a –LR of 0.2 lowers the posttest probability to less than 2% and a D-dimer assay with a –LR of 0.1 lowers the posttest probability to less than 1%.

Five major types of D-dimer assays are available: enzyme-linked immunosorbent assay (ELISA), latex agglutination assay, whole blood assay, turbidimetric assay, and immunofiltration assay. Pooled analysis of published studies demonstrate that ELISA D-dimer assays have a sensitivity for the diagnosis of PE of 97% and a specificity of 44% (+LR 1.7; –LR 0.07).[48] The drawback to conventional ELISA assays is the requirement for 2 to 4 hours to perform them.[50-67] Latex kits are rapid, but demonstrate inadequate sensitivity to reliably exclude PE in multiple studies (pooled sensitivity=70% and specificity=76%; +LR 3.0; –LR 0.38).[48,58,59,64-71] A qualitative whole blood assay appears promising, with a pooled sensitivity of 89% and 59% specificity in detecting PE (+LR 2.2; –LR 0.18).[48,50,60,72-75] The qualitative whole blood assay requires 5 minutes to perform and reliably excludes PE when used with the Wells et al[41,76] clinical model to estimate pretest probability of PE (negative predictive value 99.5%). One recent study has called into question the negative predictive value of the qualitative whole blood assay with a sensitivity of 68% and negative predictive value of 83% for PE.[77] However, this study had a high prevalence of PE and an unusually high reported specificity of the assay that may account for the findings.[78] Two rapid, quantitative D-dimer tests are available that can give a result within 2 hours: the rapid ELISA[79-82] and the turbidimetric assays.[83-87] Both of these assays offer a sensitivity above 95% and a negative likelihood ratio of approximately 0.07 at a cutoff value of 500 ng/mL.[43] The immunofiltration D-dimer test also holds promise for ED use because these assays can be used at the bedside and provide test results within 10 minutes. These assays are referred to as "silk-screen assays" and work much like the well-known qualitative urine pregnancy tests that are commonly used in EDs. Preliminary studies show that these rapid tests have sensitivity comparable to the quantitative rapid ELISA assay, with a pooled sensitivity of 95% and specificity of 33% (+LR 1.4; –LR 0.15).[48] Because of their diagnostic accuracy and rapid turnaround time, either of the latter assay types appears well suited for use by the ED.

Patient Management Recommendations: Can a negative D-dimer exclude PE?

Level A recommendations. None specified.

Level B recommendations. In patients with a low pretest probability of PE, use the following tests to exclude PE:

1. A negative quantitative D-dimer assay (turbidimetric or ELISA).
2. A negative whole blood cell qualitative D-dimer assay in conjunction with a Wells' score of 2 or less.

Level C recommendations. In patients with a low pretest probability of PE, negative findings on a whole blood D-dimer assay (when not used with Wells' scoring system) or immunofiltration D-dimer assay can be used to exclude PE.

II. When can V/Q scan alone or in combination with venous ultrasonography and/or D-dimer exclude PE?

For approximately 2 decades, the radioisotopic V/Q scan has been the most widely accepted test to screen for PE in the ED. The justification for the primary use of the V/Q scan originates from the National Institutes of Health–sponsored, multicenter, PIOPED study, which was originally published in 1990[88] and was later updated with additional data.[89-91] In the initial PIOPED analysis, the posttest rates of PE for the nuclear scan reports "high," "intermediate," "low," and "near normal/normal" were 87%, 30%, 14%, and 4%, respectively. The

negative likelihood ratio for the "near normal/normal" scan for PE was approximately 0.1, and the positive likelihood ratio for a "high probability" scan was 18.3.[92] Thus, if the pretest probability is below 20%, PE can be excluded with reasonable certainty and a "near normal/normal" scan. On the other hand, in patients with a pretest probability of 20% or higher, a "high probability" scan can be used to diagnose PE with reasonable certainty. Unfortunately, 60% of the PIOPED patients with PE had a V/Q scan read as "low" or "intermediate" probability (collectively known as "nondiagnostic" scans) that cannot be used to identify or exclude PE without corroborative information. In particular, the clinical probability of PE (based on clinical criteria that included history, risk factors for PE, and physical findings) was found to markedly alter the posttest probability of PE. For example, in patients with low probability V/Q scans, rates of PE in patients with low, intermediate, and high clinical probability of PE were 4%, 16%, and 40%, respectively.[88]

Several outcome studies have demonstrated an incidence of less than 1% of subsequent PE on long-term follow-up in patients with a normal V/Q scan in whom anticoagulation was withheld.[93,94] The authors of these studies have suggested that a normal V/Q scan excludes PE in all patients regardless of pretest probability. However, only one of these studies reported pretest probability of patients, and this study was limited by the fact that only 40 of the patients were in the high-risk subgroup.[94] Other outcome studies have also questioned the grouping of a low probability scan into the "nondiagnostic" category. In a retrospective study, Rajendran and Jacobson[95] investigated 536 patients with a low probability V/Q scan and found no patients with evidence of PE on 6-month follow-up.

Because asymptomatic venous thrombosis is found in a significant number of patients with confirmed symptomatic PE (most commonly in the proximal leg),[1,6] a common practice to help reduce the probability of PE in patients with nondiagnostic V/Q scans is to obtain duplex ultrasonography of the lower extremities with the logic that, if a DVT is discovered, this will provide defacto evidence of the presence of a PE.[39,93,94]

Conversely, a negative ultrasonographic scan finding is thought to significantly lower the probability that PE is present in patients with nondiagnostic lung scans. However, sensitivity of a single lower-extremity venous ultrasonography for PE in patients with a nondiagnostic V/Q scan is approximately 50%.[96,97] Thus negative findings in a single lower-extremity ultrasonographic scan should not be used to exclude PE in patients with a non-low pretest probability and a nondiagnostic V/Q scan.

A growing body of class II evidence indicates that the negative likelihood ratio for PE of most new generation D-dimer assays is less than the negative likelihood ratio for PE of a single negative bilateral lower extremity duplex Doppler ultrasonographic scan. The combination of a low-to-moderate clinical suspicion, plus a nondiagnostic V/Q scan (prevalence of PE 12% to 30%) and a negative finding on a quantitative (turbidimetric or ELISA) D-dimer assay or a negative finding on a qualitative whole blood D-dimer assay in conjunction with a Wells' score of 4 or less, reliably excludes PE.[45,53-55,74-76]

In patients with a high pretest probability of PE and a normal or nondiagnostic scan, there is insufficient information to offer a definitive clinical protocol to proscribe the evaluation. Studies are limited by the low number of high-risk patients and protocols that are highly dependent on institutional resources.[9-12,39,47,48,55,68,70,76,95-98] The necessary corroborative studies (eg, lower-extremity duplex Doppler ultrasonography, D-dimer assay, spiral CT scan, venogram), versus proceeding to pulmonary angiography versus excluding the diagnosis of PE must be driven by the clinical circumstances, institutional resources, and pretest probability.

Patient Management Recommendations: When can V/Q scan alone or in combination with venous ultrasonography and/or D-dimer assay exclude PE?

Level A recommendations. In patients with a low-to-moderate pretest probability of PE, a normal perfusion scan reliably excludes clinically significant PE.

Level B recommendations. In patients with a low-to-moderate pretest probability of PE and a non-diagnostic

V/Q scan, use 1 of the following tests instead of pulmonary arteriogram to exclude clinically significant PE:

1. A negative quantitative D-dimer assay (turbidimetric or ELISA).
2. A negative whole blood cell qualitative D-dimer assay in conjunction with a Wells' score of 4 or less.
3. A negative single bilateral venous ultrasonographic scan for low-probability patients.
4. A negative serial* bilateral venous ultrasonographic scan for moderate-probability patients.

Level C recommendations. In patients with a low-to-moderate pretest probability of PE and a nondiagnostic V/Q scan, use a negative whole blood D-dimer assay (when not used with Wells' scoring system) or immunofiltration D-dimer assay to exclude PE.

III. Can spiral CT replace V/Q scanning in the diagnostic evaluation of PE?

The spiral CT angiogram has gained recognition as a rapid method of evaluating patients for PE. It is especially useful in patients who have conditions that result in nondiagnostic V/Q scans (ie, patients with significant cardiopulmonary disease, patients with chronic obstructive pulmonary disease, patients with infiltrates on chest radiography).[11,47-49] The examination requires the patient to lie supine and hold their breath for a few seconds and requires intravenous injection of approximately 100 mL of contrast material. In a recent meta-analysis, the pooled sensitivity of 9 prospective spiral CT studies was approximately 77%, and the pooled specificity of spiral CT was approximately 89%.[48,99-117] The diagnostic sensitivity of spiral CT is generally 95% or higher for segmental or larger PEs, but is approximately 75% for subsegmental PE.[104-106] Evolution in technology is occurring at such a rapid pace that subsegmental PE are now being visualized by thin collimation multidetector row spiral CT scanners with 1- to 2-mm image reconstruction. Preliminary studies suggest that these new generation CT scanners will have an even higher sensitivity and specificity for detection of PE.[118-120] The PIOPED II study, which is an ongoing multicenter prospective study using newer generation CT scanners, should provide a greater understanding of the diagnostic utility of CT pulmonary angiogram. A protocol that includes image slices through the thighs and pelvis during the venous return phase (CT venography) to examine for DVT may be helpful for diagnosis of patients with significant venous thromboembolic disease.[113,121] In a recent study of 541 consecutive patients who underwent CT pulmonary angiography for suspected PE (17% positive for PE on CT scan), Cham et al[121] reported the findings of proximal DVT on CT venography in 16 patients with negative findings on CT pulmonary angiogram. The authors conclude that CT venography in conjunction with CT angiography identified an additional 18% of patients deserving treatment and, thus, has potential to have a significant effect on patient care.

Outcome data indicate that negative findings on a CT scan reliably exclude clinically significant PE.[122-126] Goodman et al[122] in a nonrandomized prospective trial compared 198 patients with negative findings on a CT scan to 188 patients with a normal or low probability V/Q scan for 3-month outcome. Patients undergoing CT scanning had more severe disease, more PE risk factors, and longer hospital stays. Incidence of subsequent PE was 1% in patients with negative findings on a CT scan, 0% in patients with normal findings on a V/Q scan, and 3% in patients with a low-probability V/Q scan. In the largest study to date, Swensen et al[126] retrospectively studied 1,512 consecutive patients undergoing CT angiography for suspected PE for 3-month outcome. The incidence of DVT or PE on follow-up was 0.5% and fatal PE 0.3% in the 1,010 patients with negative findings on a spiral CT scan. One particular advantage of CT angiogram over V/Q scan is that an alternative diagnosis is identified in a significant number of patients.[49,99,101,103,116]

Patient Management Recommendations: Can spiral CT replace V/Q scanning in the diagnostic evaluation of PE?

Level A recommendations. None specified.

*Serial venous ultrasonography refers to scheduling a patient for follow-up examination in the ED within 3 to 7 days or referring to a primary care physician for follow-up.

Level B recommendations. Thin collimation spiral CT scan of the thorax with 1- to 2-mm image reconstruction may be used as an alternative to V/Q scan during the diagnostic evaluation of patients with suspected PE.

Level C recommendations. Spiral CT scan of the thorax with delayed CT venography may be used for increased detection of patients with significant thromboembolic disease.

IV. What are the indications for fibrinolytic therapy in patients with PE?

As in the treatment of patients with acute coronary syndromes, one must make a risk-benefit decision when considering fibrinolytic treatment in patients with PE. A meta-analysis of 5 studies on fibrinolytic therapy in PE found an intracranial hemorrhage rate of 2% with a mortality rate of 0.5%.[127] Diastolic hypertension was the principle risk factor in predicting development of intracranial hemorrhage. It is estimated that the overall mortality from symptomatic PE is 10%, with age older than 70 years, congestive heart failure, chronic obstructive lung disease, presence of cancer, hypotension, tachypnea, and right ventricular hypokinesis all being associated with increased mortality.[1,128]

Data from clinical trials and consensus reports of fibrinolytic agents to treat PE reveal only one major indication for treatment, namely patients who are hemodynamically unstable, especially in the presence of persistent systemic hypotension.[1,9,12,129-140] Jerjes-Sanchez et al[130] found a significant mortality reduction in patients with PE complicated by cardiogenic shock who were treated with streptokinase plus heparin compared with patients randomized to receive heparin only. A controversial issue is whether or not right ventricular (RV) dysfunction as demonstrated on echocardiography should be considered a criterion for fibrinolytic therapy.[140-142] Although it is well established that patients with RV dysfunction observed on echocardiography who are treated with fibrinolytic therapy have more rapid return of RV function and restoration of pulmonary perfusion, these improvements have not translated to improved mortality in the absence of shock.[129-133,140-145] Other factors that may compel consideration for fibrinolytic administration are a preexisting history of congestive heart failure, pulmonary hypertension, previous history of large PE, hypoxia, and patients with only one lung.[1,9-12,136]

In an unstable patient with suspected PE, the main controversy is whether to administer fibrinolytic therapy on the basis of high clinical probability or whether specific imaging is required. If the patient is too unstable for lung imaging, findings of RV dysfunction on bedside echocardiography may be used as defacto evidence for PE and thus prompt one to consider fibrinolytic administration.[129-133] The "window" to safe and effective PE fibrinolysis is 14 days.[129] The US Food and Drug Administration has approved 3 regimens to treat PE: (1) streptokinase (250,000 U bolus, followed by 100,000 U/h for 24 hours); (2) urokinase (1,000 U/kg for 10 minutes, followed by 1,000 U/kg/h for 24 hours—currently unavailable in the United States); (3) recombinant tissue plasminogen activator (rt-PA) (100 mg infused over 2 hours).

Patient Management Recommendations: What are the indications for fibrinolytic treatment in patients with PE?

Level A recommendations. None specified.

Level B recommendations. Consider fibrinolytic therapy in hemodynamically unstable patients with confirmed PE.

Level C recommendations. Consider fibrinolytic therapy in:

1. Hemodynamically stable patients with confirmed PE and RV dysfunction on echocardiography.
2. Unstable patients with high clinical index of suspicion (especially if RV dysfunction can be demonstrated on bedside echocardiography).

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APPENDIX A.

Literature classification schema.[*]

Design/ Class	Therapy[†]	Diagnosis[‡]	Prognosis[§]
1	Randomized, controlled trial or meta-analyses of randomized trials	Prospective cohort using a criterion standard	Population prospective cohort
2	Nonrandomized trial	Retrospective observational	Retrospective cohort Case control
3	Case series Case report Other (eg, consensus, review)	Case series Case report Other (eg, consensus, review)	Case series Case report Other (eg, consensus, review)

[*]Some designs (eg, surveys) will not fit this schema and should be assessed individually.
[†]Objective is to measure therapeutic efficacy comparing ≥2 interventions.
[‡]Objective is to determine the sensitivity and specificity of diagnostic tests.
[§]Objective is to predict outcome including mortality and morbidity.

APPENDIX B.

Approach to downgrading strength of evidence.

	Design/Class		
Downgrading	**1**	**2**	**3**
None	I	II	III
1 level	II	III	X
2 levels	III	X	X
Fatally flawed	X	X	X