The diagnostic procedure for subjects with suspected pulmonary embolism. A recent comparison among the recommendations available from the international guidelines

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ABSTRACT

Acute pulmonary embolism (PE) is a common and potentially life-threatening disease characterized by the occlusion of arterial lung vasculature, typically due to thrombi traveling from a thrombotic vein in the lower limb. Several guidelines have been proposed worldwide to assist clinicians in its diagnosis, however, they are not consistent on the usage of diagnostic tools. This commentary reviews the literature and discusses the concordance/discordance between these international guidelines on PE diagnosis.

Introduction

Acute pulmonary embolism (PE) is characterized by the occlusion of arterial lung vasculature typically due to thrombi traveling from a thrombotic vein in the lower limb. It is a frequently occurring and potentially life-threatening disease.[1] The term venous thromboembolism (VTE) encompasses PE and/or deep vein thrombosis (DVT). The incidence of PE is approximately 1 in 1000 persons per year;[2] however, it increases sharply with age, reaching 11.3 per 1000 people aged 80 years or older.[3] Overall, the incidence of VTE is slightly higher in men than in women, at exception of women under 45 years of age, due to the risk related to estrogen therapy and pregnancy,[4] and over 80 years in whom an excess of PE-related mortality has been reported.[5]

Clinical manifestations of PE may vary widely, ranging from entirely asymptomatic forms (as is the case of silent PE in 30-50% of patients with confirmed DVT),[6-8] to extremely serious, and life-threatening illness. Between the two extremes lie most patients, who have symptomatic, non-high-risk PE. Common symptoms of PE are fatigue, chest pain, short of breath, cough, hemoptysis, and syncope; more recently, even occurrence of dyspnea on exertion was detected as potential symptom of PE.[9] However, the symptoms are non-specific for PE, and may be present in several different clinical conditions.

Clinical presentation of patients with suspected PE is therefore highly variable. What is important is to tailor initial therapeutic and diagnostic management of patients according to the recommended classification of disease severity,[10] which categorizes early mortality risks (in-hospital or 30 days) as: high, intermediate (high or low), and low. Anticoagulation with fast-acting drugs should be initiated in patients at high (hemodynamic instability) or intermediate risk, even before diagnostic test results are known. A recent study (the COPE study),[11] investigating a cohort of >5200 patients with acute PE, found an in-hospital mortality of 3.4%, and a 30-day mortality of 4.8%, mostly due to associated co-morbid conditions. Patients categorized at low severity risk may follow the diagnostic procedures without immediate anticoagulation.

All patients with suspected PE need a diagnosis confirming the presence or not of the disease. This is necessary since a high risk of early mortality has been reported when PE is left untreated.[12] However, treating with anticoagulants subjects who do not have PE is associated with a significant and needless risk of bleeding and may delay the diagnosis of the real cause of symptoms. Diagnostic management of hemodynamically stable patients with suspected PE (95-98% of all patients), aimed at ruling out the disease, does however present several challenges. The increasing awareness of the risks associated with PE, the wider availability of less-invasive imaging tests (computed tomography pulmonary angiography, CTPA), and the greater sensitivity of physicians towards PE are all factors favoring a larger recourse

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to diagnostic workup for PE, resulting in overutilization of imaging tests and a lower rate proportion of PE diagnosis in suspected patients. As an example, a retrospective observational study, performed on 8449 patients who underwent CTPA, showed that more than 99% of CTPA resulted negative.[13] Inappropriate use of CTPA can be deleterious leading to adverse complications like contrast-induced allergic and non-allergic pathologies (especially contrast-induced nephropathy) and increased healthcare costs.[14,15] Furthermore, exposure to ionizing radiation and increased risk of cancer due to radiation need to be taken into account.[16]

An approach that combines different diagnostic tests according to well validated algorithms is the only solution to the above-mentioned diagnostic problems. Several international guideline recommendations have been proposed to help clinicians in PE diagnosis. Unfortunately, not all of them are always concordant on how to use the various diagnostic tools.

Falster *et al.*[17] have recently published a comparison of international guideline recommendations regarding the diagnosis of PE. In their extremely valuable work, the authors compared the content of 13 international guidelines (listed in *Supplementary Materials*), authored by scientific medical societies or expert author groups. The authors particularly focused on the assessment of pretest probability, D-dimer testing interpretation, empirical treatment before diagnosis, and diagnostic imaging. The authors also provided an overview of the diagnostic pathways proposed by each guideline.

The present commentary aims to go through the above-mentioned article, highlighting the points of concordance/discordance among the international guidelines on PE diagnosis.

Clinical presentation

The initial clinical evaluation of a patient with suspected PE includes risk factor consideration, physical examination, blood tests, ECG monitoring and chest radiographs. These items are nonspecific for PE diagnosis, but the evaluation is of considerable value since it signals whether the patients may have an acute PE. Furthermore, this first diagnostic approach is essential for identifying subjects with suspected PE who are at high risk of early mortality (hemodynamic instability or right ventricular dysfunction) and need fast diagnosis and therapy. Thankfully, most patients are not in this situation and, after suspected PE is confirmed, should undergo pretest probability assessment.

Assessment of pretest probability

Assessment of PE probability before performing specific tests may avoid unnecessary testing and is critical for interpretation of test results. To this end, the use of validated clinical prediction rules (summarized in Table 1) is recommended. The Wells rule consists of 7 variables,[18] including a judgment of whether PE is the most likely diagnosis. The revised Geneva score includes similar items except for a clinical subjective judgment on the likelihood of PE.[19] The presence of subjective clinical judgment in the Wells rule is the main difference between the two tests and may end up overemphasizing the role of subjective judgment when using Wells. Though clinical studies and meta-analyses have reported comparable predictive accuracies of the two tests,[20,21] guideline indications differ. The Wells rule is recommended by all guidelines except for ACEP and JCS, while the revised Geneva score is recommended by 9 guidelines (UpToDate, ESC/ERS, EANM, PERT, ACEP, ASH, ACP, SPAIN, BTS). While physician gestalt has been shown to be useful in predicting pretest probability in suspected PE subjects,[22] the use of clinical gestalt is recommended by only 5 guidelines (UpToDate, ESC/ERS, ACP, JCS, and PIOPED II.

The Pulmonary Embolism Rule out Criteria (PERC) has been recommended to reduce the need for further testing in subjects with low pretest probability of PE.[23] PERC includes 8 items (Table 1) and if none of them is present in subjects with low pretest probability (<15%), then the probability of false negative results is so low (the predefined threshold is <1.8%) that further testing becomes unnecessary. Although PERC was subsequently validated by a larger, prospective, multicenter clinical study,[24] its inclusion to assess pretest probability is recommended by only 8 of the guidelines.

Empirical treatment before pulmonary embolism diagnosis

As already said, to avoid early mortality and recurrent VTE and death at three months,[25] patients with suspected PE may need to start anticoagulant treatment before final diagnosis. Only some of the guidelines give recommendations on this issue. Furthermore, when reported, the recommendations present a high degree of heterogeneity with low levels of proof due to the general lack of scientific data on the matter. The initiation of anticoagulant treatment in all patients with suspected PE, irrespective of pretest probability, is recommended by 3 guidelines (with some differences in relation to Wells' score and time needed for D-dimer results; NICE, EANM, and JCS). Four guidelines recommend treatment only in patients with high or intermediate probability (ESC/ERS, SPAIN, PIOPED II, and BTS), one recommends treatment only in patients with high probability, though after having carefully considered bleeding risk (PERT) while 4 give no recommendation in this regard (THANZ, ACEP, ASH, and ACP). In conclusion, scientific data on empirical treatment before PE diagnosis are lacking with only some guidelines providing recommendations on the matter (with light differences). New clinical studies on this subject are warranted.

D-dimer testing

After assessment of pretest probability, D-dimer assay is largely used for the work up of VTE exclusion. A large variety of assays are available for clinical use. In most cases they have a sensitivity above 95% and have been approved by the Food and Drug Administration for VTE exclusion thanks to their high negative predictive value when the levels are below a certain validated threshold (then considered as negative D-dimer) in suspected subjects with low or unlikely pretest probability.[26] D-dimer levels, however, increase in all conditions associated with increased fibrin formation with non-specific positive results. The specificity of the test, generally around 50%, may decrease further in many situations (as much as 10% in elderly subjects), resulting in a high rate of false-positive results. This drawback is particularly important in the case of elderly subjects, a population with high prevalence of suspected VTE.

Table 1. Wells rule, original and simplified,[18,44] revised Geneva score,[19] and Pulmonary Embolism Rule out Criteria (PERC).[23]

Wells rule		
	Score	
Items	Original	Simplified
Previous PE or DVT	1.5	1
Heart rate >100	1.5	1
Recent surgery/immobilization	1.5	1
Clinical signs of DVT	3	1
Alternative diagnosis less likely than PE	3	1
Hemoptysis	1	1
Cancer	1	1
Total score (trichotomous)	***Estimated prevalence, %**	
<2 low probability	≈6	
2-6 intermediate	≈23	
>6 high	≈49	
Total score (dichotomous)		
PE unlikely ≤4 or ≤ 1	≈8	
PE likely >4 or >1	≈34	

Revised Geneva score	
Items	Score
Age >65 y	1
Previous PE or DVT	3
Surgery or fracture within 1 month	2
Active malignancy	2
Unilateral lower limb pain	3
Hemoptysis	2
Heart rate ≥75 ≥95	3 5
Pain on lower limb palpation and unilateral edema	4
Total score	***Estimated prevalence, %**
<4 low probability	≈9
4-10 intermediate	≈26
>10 high	≈76

PERC	
Items	Score
Age ≥50 y	1
Heart rate ≥100	1
O2 saturation $\underset{\lambda}{\varsigma}$95% without supplementary oxygen	1
Unilateral leg swelling	1
Hemoptysis	1
Surgery or trauma within 4 weekstreated in general anesthesia	1
Previous PE or DVT	1
OC, hormone replacement or estrogen hormone use	1
Total score	***Estimated prevalence, %**
0	<2
≥1	≥2

PE, pulmonary embolism; DVT, deep vein thrombosis; OC, oral contraceptives.
*Values of estimated prevalence are obtained from the meta-analytic data by Ceriani *et al.*,[21] as reported in Falster *et al.*[17]

All guidelines, except for ACEP, recommend performing D-dimer assay using predefined algorithm (after pretest probability and after exclusion of other possible causes of positive results) to reduce as much as possible the number of false-positive results. The guidelines generally agree on the need to perform D-dimer testing only in subjects with low or unlikely pretest probability to avoid possible false-negative results in subjects at high probability.

Different diagnostic approaches have been proposed to increase the usefulness of D-dimer testing in suspected PE subjects. According to the *Age-Adjusted strategy,*[27] D-dimer cut-off is calculated in relation to age: in patients aged 50 years or more the age-adjusted cut-off values are calculated by multiplying the age × 10. The *YEARS strategy* suggests assessing the presence of only three items:[28] clinical signs of DVT, hemoptysis, and PE as the most likely diagnosis. If none of these are present the D-dimer threshold is increased to 1000 ng/mL. Conversely, if one or more of the above items are present the conventional cut-off should be used (500 ng/mL). Finally, the *Clinical Pretest Probability-Adjusted* strategy proposes using a D-dimer cut-off of 1000 ng/mL in subjects with a low pretest probability,[29] whereas in patients with moderate pretest probability, the conventional cut-off (500 ng/mL) is used. These diagnostic approaches aim to lower the number of CTPA needed, particularly in subjects at low pretest probability, but clearly have an inherent risk of false-negative results.

As expected, the guidelines differ on this issue. Of the nine guidelines published after 2014, seven (NICE, ESC/ERS, EANM, PERT, ACEP, ASH, and ACP) recommend the adoption of the age-adjusted strategy; the THANZ does not give any recommendation on D-dimer cutoff, whereas the UpToDate prefers the conventional cutoff while also considering the age-adjusted cutoff, but only in subjects with low pretest probability. The YEARS strategy is endorsed by ESC/ERS and PERT. All the guidelines published before 2014 (SPAIN, JCS, PIOPED II, and BTS) recommend using the conventional cutoff.

Diagnostic investigation by echocardiography

The utility of echocardiography in a hemodynamically stable patient with suspected PE is controversial and signs of right ventricular strain [including ventricular dilatation, septal deviation towards the left ventricle (D-sign) and akinesia of the right ventricular free wall (McConnell's sign)] cannot be considered as indicative of PE. Only one guideline (ESC/ERS) considers the finding of a right heart thrombus as confirmation of PE diagnosis. Eight guidelines (UpToDate, ESC/ERS, EANM, PERT, SPAIN, JCS, PIOPED II, and BTS) agree that echocardiography is useful in hemodynamically unstable suspected PE patients and that finding right ventricular strain in these patients supports fibrinolytic treatment.

Ultrasound diagnosis of deep vein thrombosis

DVT and PE are both VTE manifestations and generally require identical treatment; furthermore, silent PE can be detected in a large number of DVT (especially proximal).[6] For these reasons, the detection of DVT in subjects with suspected PE is accepted as indicative of PE by 5 guidelines (ESC/ERS, PERT, ACP, PIOPERD II, and BTS) which recommend stopping any further investigation after DVT diagnosis. Three other guidelines (UpToDate, ASH and SPAIN) recommend PE diagnosis be accepted in the presence of DVT, but only if previous PE imaging tests are inconclusive.

Diagnostic imaging

The guidelines generally agree that patients with suspected PE who i) are at low/intermediate clinical probability and have altered D-dimer levels, or ii) have high clinical probability, should undergo final diagnostic imaging. The quality of CT scanners has improved enormously in recent years and radiologists are now better equipped to distinguish between contrast filling defects in the peripheral pulmonary vasculature that are real subsegmental PE from flow artifacts that are not PE or that require anticoagulation.[30] Guidelines differ on the need for VQ scan versus CTPA. Some guidelines (ESC/ESR) question reaching any clinical conclusion when CTPA is negative in subjects at high clinical probability and recommend completing the investigation with VQ scan. Conversely, other guidelines (PERT, THANZ, JCS, ACP and BTS) accept the exclusion of PE when CTPA is negative even in subjects at high clinical probability.

Conclusions

The diagnosis of PE is an extremely important clinical activity because it involves an ever-increasing number of subjects in whom this disease is suspected. Since – in the end – many of them will not have the disease, the diagnostic procedure should be a balancing act between keeping the use of imaging tests (not always without side-effects) as low as possible and recognizing the need to reach a definitive diagnosis. The serious and potentially fatal consequences of false negative decisions highlight the importance of using standardized diagnostic approaches that have been proved to provide the best results in term of reducing useless (and potentially harmful) tests and keeping clinical false negatives as low as possible. As such, all the currently available international guidelines recommend following a diagnostic procedure based on i) assessment of pretest clinical probability using a validated score [Wells score for PE or the revised Geneva score (low/intermediate or high)] followed by ii) D-dimer testing but only in case of low/intermediate pretest clinical evaluation and finally, iii) the use of CTPA in subjects with low/intermediate clinical probability, who also have positive D-dimer results, and subjects with high probability (without D-dimer assay). Furthermore, some strategies have been proposed aimed at increasing the specificity of the assay, based on the use of higher D-dimer cutoff levels in relation to age (*age-adjusted strategy*), pretest probability (*clinical pretest probability-adjusted strategy*) and absence of three specific clinical signs (*YEARS strategy*). During this process, other issues may emerge, such as the need for anticoagulation to protect patients before any final diagnosis is reached.

As is to be expected, not all the international guidelines agree on all the points and only the more recent one can be updated with the results of recent clinical studies.

The article by Falster *et al*.[17] is a cornerstone for comparing the currently available international guidelines on PE diagnostic procedure. The authors highlight the differences between the guidelines and provide a very useful visual summary of the testing recommended by each guideline for subjects with suspected PE. Furthermore, they analyze the important points still open to debate and recommend future clinical studies be carried out in this regard.

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Online supplementary material:
List of compared international guidelines (the more recent first) with references, the acronyms in brackets.