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Suspected Acute Pulmonary Embolism: Gestalt, Scoring Systems, and Artificial Intelligence

Delphine Douillet, MD[1] Pierre-Marie Roy, MD, PhD[1] Andrea Penaloza, MD, PhD[2]

[1] Emergency Department, Angers University Hospital, INSERM 1083, Health Faculty, UNIV Angers, F-CRIN INNOVTE, Angers, France
[2] Emergency Department, Cliniques Universitaires Saint Luc, UCLouvain, F-CRIN INNOVTE, Brussels, Belgium

Address for correspondence Delphine Douillet, MD, Département de Médecine d'Urgence, Centre Hospitalier Universitaire d'Angers, 4 rue Larrey 49100 Angers, France (e-mail: delphinedouillet@gmail.com).

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Abstract

Pulmonary embolism (PE) remains a diagnostic challenge in 2021. As the pathology is potentially fatal and signs and symptoms are nonspecific, further investigations are classically required. Based on the Bayesian approach, clinical probability became the keystone of the diagnostic strategy to rule out PE in the case of a negative testing. Several clinical probability assessment methods are validated: gestalt, the Wells score, or the revised Geneva score. While the debate persists as to the best way to assess clinical probability, its assessment allows for the good interpretation of the investigation results and therefore directs the correct diagnostic strategy. The wide availability of computed tomography pulmonary angiography (CTPA) resulted in a major increase in investigations with a moderate increase in diagnosis, without any notable improvement in patient outcomes. This leads to a new challenge for PE diagnosis which is the limitation of the number of testing for suspected PE. We review different strategies recently developed to achieve this goal. The last challenge concerns the implementation in clinical practice. Two approaches are developed: simplification of the strategies versus the use of digital support tools allowing more sophisticated strategies. Artificial intelligence with machine-learning algorithms will probably be a future tool to guide the physician in this complex approach concerning acute PE suspicion.

Keywords
- pulmonary embolism
- gestalt
- computerized tomography pulmonary angiogram
- D-dimer
- decision rule
- decision-making
- diagnosis
- risk assessment models
- scores
- artificial intelligence

Pulmonary embolism (PE) is a frequent condition and remains a diagnostic challenge for emergency physicians. With around 300,000 PE-related deaths each year in the United States,[1] PE represents the third most common cause of cardiovascular mortality.[2,3] As signs and symptoms are very common and nonspecific, further examinations are classically required to rule in or rule out the diagnosis. Historically, the gold standard was pulmonary angiography but this examination was associated with a 6.5% rate of adverse events including 0.5% chance of death, leading to the development of less-invasive testings.[4] The first tests were the ventilation-perfusion (V/Q) scan and D-dimer, but their diagnostic performances were insufficient to allow their use as stand-alone tests. However, on the basis of the Bayesian approach, they could accurately exclude or confirm PE in specific ranges of PE prevalence, that is, pretest clinical probability.[5]

Over time, the ability of physicians to categorize patients suspected of PE into high, moderate, or low pretest clinical probability was demonstrated, both using their implicit global assessment (gestalt), or dedicated prediction rules.[6] Therefore, clinical probability assessment has become a keystone of the PE diagnostic process, especially to rule out PE with confidence in case of a negative test. It is the first step of the currently recommended diagnostic strategies with a view to defining test ordering and interpreting its result (►**Fig. 1**).

In the last decades, probably due to the wide availability of computed tomography pulmonary angiography (CTPA), as

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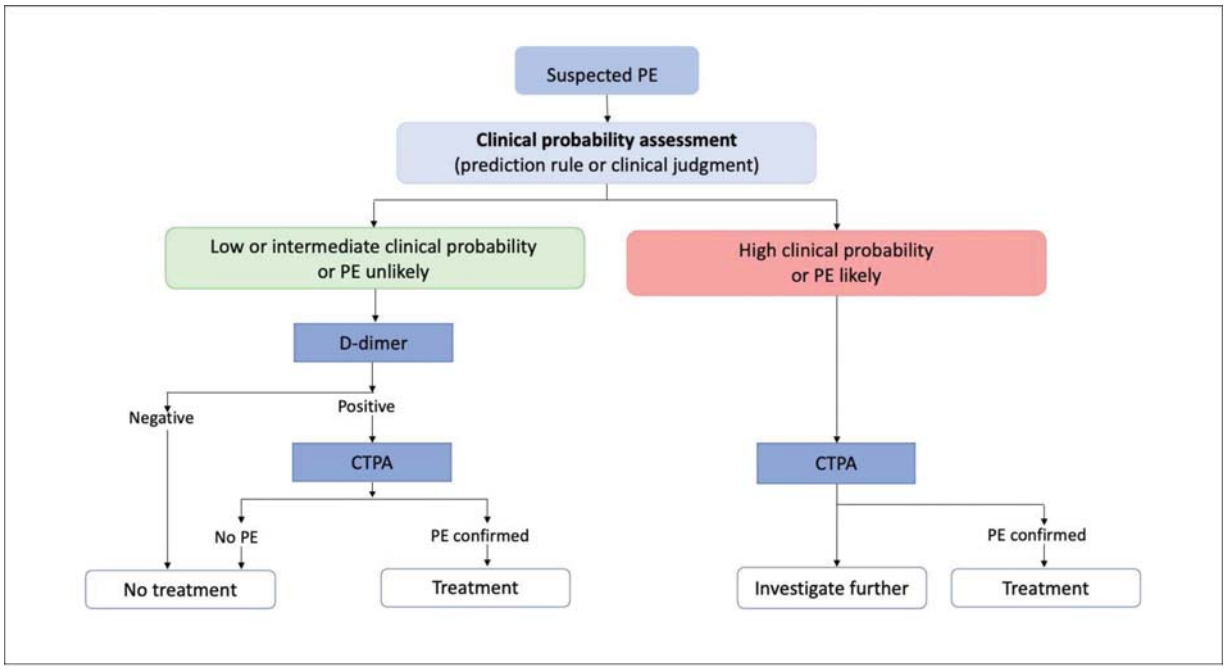

Fig. 1 Clinical probability assessment has become a keystone of the PE diagnostic process, particularly, to rule out PE with confidence in the setting of negative testing. It is the first step of currently recommended diagnostic strategies. CTPA, computed tomography pulmonary angiography; PE, pulmonary embolism.

well as medicolegal fears, a major increase in patients investigated for suspected PE was observed in the United States. It was associated with a moderate increase in PE diagnosis without any notable improvement in patient outcomes.[7–10] The same overtesting was more recently observed in Europe, as demonstrated by the decrease in PE prevalence in the more recent studies (12–14%), compared with 20 to 30% in the last decade, and 50% in the early 1980s.[11–15] These findings lead to a new challenge for PE diagnosis: the limitation of the number of tests for suspected PE and, especially, the number of CTPAs. The final goal is to limit the adverse effects of the overtesting and overdiagnosis of PE, namely, ionizing radiation and induced cancer, nephrotoxicity of iodine contrast, bleeding due to anticoagulation for clinically nonrelevant PE, and financial cost.[16–19] Different strategies for achieving this goal were recently proposed.[20–24]

Finally, the last challenge concerns the implementation of validated diagnostic strategies based on clinical probability assessment in current practice. Two options are currently investigated, namely, the definition of simplified and perhaps more memorable rules versus the use of digital support tools allowing more sophisticated and perhaps more accurate rules. For the latter, artificial intelligence (AI) may be an important and promising tool. In this review, we discuss the place of clinical probability over time for optimizing the diagnostic process for suspected PE.

Clinical Probability

Gestalt

Until the end of the 1980s, physicians always used their overall gestalt to suspect PE and to order further examinations. In 1990, the prospective investigation of pulmonary embolism diagnosis (PIOPED) investigators demonstrated that physicians were able to categorize suspected PE patients into high, moderate, or low pretest clinical probability based on the implicit clinical assessment and nonspecific examinations (chest X-ray, electrocardiogram, and blood gas).[11] The discrimination of this categorization was assessed by using angiography as the gold standard. Moreover, this study showed the value of combining this clinical judgment and the V/Q scan results, thereby applying the Bayesian approach. This approach was proven to be valid in subsequent diagnostic studies by improving the reliability of diagnostic examinations.[25–27] Rodger et al found low reproducibility of the gestalt clinical probability assessment, with a correlation coefficient kappa of 0.33.[28] These findings have led to the search for other clinical probability assessment methods.

Scoring Systems

At the beginning of the century, explicit scores were developed to standardize and to improve the applicability and reproducibility of clinical probability assessment. These scores allow the classification of patients into three categories (low, intermediate, and high clinical probability) or two categories (likely or unlikely). The best validated and most widely used scores are the Wells score and the revised Geneva score (►**Table 1**).[29,30] In contrast to the revised Geneva score, which is fully standardized, the Wells score includes a subjective variable: "alternative diagnostic less likely than PE." Both prediction rules have been simplified to increase their adoption into clinical practice. External validation exhibits high reliability for patients in the emergency room.[31–34] Irrespective of the score used, the proportion of patients with confirmed PE can be expected to be approximately 10% in the low, 30% in the moderate, and 65% in

Table 1 Clinical probability scores

Criterion	Wells	RGS	PERC	YEARS	4PEPS
Age (y)					
<50					−2
50–64					−1
≥ 50			1		
>65		1			
Male sex					1
Surgery of immobilization within the past 4 weeks	1.5	2	1		2
Chronic respiratory disease					−1
Cancer	1	2			
Personal history of VTE	1.5	3	1		1
Hormonal estrogenic treatment			1		2
Hemoptysis	1	2	1	1	
Syncope					2
Chest pain and acute dyspnea					1
Clinical signs of DVT	3			1	3
Unilateral lower limb pain		3			
Pain on lower limb deep vein palpation and unilateral edema		4	1		
Heart rate (bpm)					
75–94		3			
<80					−1
≥ 95		5			
>100	1.5		1		
Pulse oxygen saturation $<95\%$			1		3
Alternative diagnosis less likely than PE	3			1	5
Clinical probability					
Very low (exclusion threshold)	–	–	0		<0
Low	0–1	0–3		0	0–5
Intermediate	2–6	4–10		≥ 1	6–12
High	≥ 7	≥ 11			≥ 13

Abbreviations: 4PEPS, four-level pulmonary embolism clinical probability score; bpm, beats per minute; DVT, deep vein thrombosis; PE, pulmonary embolism; PERC, PE rule-out criteria; RGS, revised Geneva score; VTE, venous thromboembolism.

the high clinical probability.[35] In the current main diagnostic strategy (►**Fig. 1**), clinical probability is first used to decide whether or not to order the D-dimer test. In patients with non–high clinical pretest probability, a negative D-dimer test, that is, <500 µg/L with a quantitative highly sensitive assay, excludes PE with a risk of false negative of less than 2%.[36,37] In patients with high clinical suspicion, the D-dimer result is not reliable as the posttest probability is always above 5%. Imaging testing is required rather than performing the D-dimer test.

However, explicit scores have their limitations. They are based on a limited number of simple variables, which limits their accuracy and results in a loss of performance. The superiority of scores over the implicit assessment remains a matter of debate.[11,25,38–41] Obviously, implicit judgment allows taking into account the whole complexity of each situation by evaluating a larger panel of risk factors. Kabrhel et al suggest that most of the predictive power of the Wells score lies in its subjective criterion, namely, that of "Are alternative diagnoses less likely than pulmonary embolism?."[42] Based on data from 723 consecutive patients with suspected PE and following a logistic regression model including the items from the Wells score, this criterion had an odds ratio (OR) of 3.30 (95% confidence interval [CI]: 1.56–6.99). The same was observed by Roy et al in the derivation of the four-level PE clinical probability score (4PEPS).[43] This observation suggests that the subjectivity of this criterion includes the assessment of a large number of other variables not taken into account in the score.[44] In a retrospective study, gestalt assessment seemed to perform better than clinical decision rules mainly because of a better selection of patients with low and high clinical probability. The area under the curve (AUC) was 0.81 (95% CI: 0.78–0.84), 0.71 (95% CI: 0.68–0.75), and 0.66 (95% CI:

0.63–0.70) for gestalt, the Wells score and the revised Geneva score, respectively.[40] The fear of some authors lies in the difficulty of implicitly assessing the clinical probability for less experienced physicians, arguing that standardized scores are easier and more reliable for clinicians lacking substantial experience.[45] However, after short training, Kabrhel et al demonstrate good discrimination regardless of the physicians' age, even if accurate determination of the clinical probability appears to improve with clinical experience.[46] These scores should not be used in some clinical situations (i.e., patients excluded from derivation and validation studies; ►**Table 1**). This is the case for pregnant patients, children, postoperative patients, etc. In these situations, the clinician's implicit assessment is usually preferred. Nevertheless, the CT-PE pregnancy studies demonstrated the reliability of the strategy based on the revised Geneva score and clinical probability, and the Artemis study demonstrated the utility of the YEARS algorithm and D-dimer to reduce the need for CTPAs in pregnant women suspected of PE.[47,48]

Beyond the performance debate as to the way to assess clinical probability, the most important message given is that each time PE is suspected, the clinical probability should be assessed to allow a good interpretation of the examination results and therefore direct the correct diagnostic strategy. The lack of an adequate strategy based on clinical probability led to an increase in thromboembolic events in the follow-up period.[49]

Strategies against Overtesting

Recently, the findings of the negative consequences of overtesting for suspected PE have led to the development of several strategies aiming to rationalize diagnostic testing. The goal of the first strategy is to answer the question concerning "in whom to suspect PE and to start a diagnostic strategy?" Classically in diagnostic studies, PE suspicion was defined as the "acute onset of new or worsening shortness of breath or chest pain without another obvious etiology."[50–54] Multiple other clinical signs or circumstances which may lead to the suspicion of PE and dyspnea together with chest pain are present in many other clinical situations.[21,52,53,55,56]

To reduce the number of "unnecessary" examinations, Kline et al derived and validated the PE rule-out criteria (PERC) which include eight criteria. The negative PERC rule, applied to low-gestalt patients, makes it possible to exclude PE without any further examination with a false negative rate of under 2% (►**Table 1**).[24]

This rule has been validated in several studies in the United States, demonstrating a risk false negative of around 1%.[24,57,58] In Europe, initial retrospective evaluation of the PERC rule was not conclusive. Used alone or in combination with a low clinical probability assessed by the Revised Geneva score, the PERC rule exhibited a false negative rate of greater than 5%.[13,59] Two recent prospective European studies, PERCEPIC and PROPER, have shown a low percentage of false-negative results, namely, 1.2% (95% CI: 0.5–2.8%) and 0.1% (95% CI: 0–0.8%), respectively.[52,53] However, due to the low overall prevalence of PE in these studies, the European Society of Cardiology (ESC) concluded that results could not currently be generalized.[60]

Another way of avoiding overtesting was explored by Douma et al by using another positivity threshold for D-dimer testing for patients over 50 years of age (i.e., age × 10).[39] This adaptation increases the clinical usefulness of the D-dimer testing and limits the number of CTPA. The ADJUST-PE study prospectively validated the age-adjusted cut-off in a cohort of 3,346 patients. Among these patients, 39.8% had a normal age-adjusted D-dimer value, thus avoiding 11.6% additional CTPA. During the 3-month follow-up period, the failure rate of this strategy was evaluated at 0.3% (95% CI: 0.1–1.7%), thus ensuring patient safety. Among patients over 75 years of age, the use of the new cut-off increased the number of patients in whom PE could be excluded based on the negative D-dimer testing from 6.4 to 30.0%, without any additional false-negative findings.[21] This adjustment has a significant impact in overcrowded emergency departments and is now recommended in ESC guidelines.[61]

Another attempt to decrease the number of CTPA performed is offered in the YEARS study. It includes three criteria which were used to assess the clinical probability: "clinical signs of deep vein thrombosis," "hemoptysis," and "PE are the most likely diagnosis." By using a D-dimer threshold of 1,000 µg/L in patients assessed as being of low clinical probability (three negative criteria), the YEARS strategy showed a decrease of 14% CTPA performed and a failure rate of 0.61% (95% CI: 0.4–1%; ►**Table 1**).[22,62] The same D-dimer level adaptation on clinical probability is proposed in the pulmonary embolism graduated d-dimer (PEGeD) study.[23] Clinical probability is assessed here by the Wells score. The D-dimer threshold of 1,000 µg/L was used in cases of low clinical probability, while the classical threshold of 500 µg/L is used for moderate clinical probability, avoiding 16% of CTPA compared with the classical strategy and a failure rate of 0% (95% CI: 0–2.9%).[63]

Recently, a new clinical probability score was derived. The 4PEPS merged all previous strategies with overtesting: ruling out PE on clinical criteria alone (PERC strategy), using 1,000 µg/L as the D-dimer cut-off in cases of low CP (PEGeD and YEARS strategy), using an age-adjusted D-dimer cut-off in cases of moderate CP (►**Table 1**). The accuracy, safety, and efficacy of the 4PEPS strategy were confirmed in two independent external validation cohorts: one with a low PE prevalence (11.7%) and one with a high PE prevalence (21.5%). The absolute reductions in imaging testing versus the standard strategy were 19 and 22% and seem higher than those experienced with the other strategies.[43] It now needs to be prospectively validated.

Implementation of These Strategies and AI

It has been demonstrated that diagnostic management of PE is often inappropriate or incomplete and leads to more than 40% chance of a harmful decision for patients.[6] Two different ways are developed: on one hand, the simplification of the clinical rules and strategies to make them easily memorable (i.e., the YEARS strategy) versus, on the other hand, the use of digital support tools allowing more sophisticated rules (i.e.,

the PEPS score). The first approach is undermined by a loss of adaptation to the patient context and had no certain increase in applicability. Recent external validation data of YEARS strategies in cohorts of European patients suggest a significant failure rate of 6.3% (17/272; 95% CI: 3.9–9.8) in the subgroup of patients with no YEARS criteria and a D-dimer of $<$1,000 ng/mL.[64] The second approach makes clinicians dependent on information technology (IT) and/or AI support and needs to be available at the exact moment when the clinicians need the information.[65] Several innovations with this purpose are about to be delivered. Roy et al developed a handheld decision-support system that has been shown to improve diagnostic decision-making for patients with suspected PE in the emergency departments.[66] Kline et al developed a web-based, clinical support instrument requiring 17 patient variables to provide a quantitative clinical probability assessment among low-risk ambulatory patients with symptoms of acute coronary syndrome and PE. This assessment was linked to better follow-up of the recommendations, and led to a significant decrease in radiation and medical cost care.[67] Recently, the prediction performance in acute PE diagnosis was evaluated using elastic net and artificial neural networks, which consider multitudes of patient-specific risk factors and dependencies in retrospective structured electronic medical record data to arrive at an imaging-specific PE likelihood recommendation. In this study, the best performing model achieved an AUC of predicting a positive PE diagnosis of 0.90 (95% CI: 0.87–0.91).[68] Machine-learning algorithms do not require linear relationships between variables, and they can analyze complex data without a preexisting hypothesis. Theoretically, such algorithm should be an ideal diagnostic tool. At the 2019 International Society of Thrombosis and Hemostasis Congress, Willan et al presented a machine-learning algorithm able to improve the risk assessment of patients referred due to suspicion of deep vein thrombosis (DVT). The algorithm was able to exclude DVT in 37.5% of patients, with no need for ultrasound (false negative rate: 0.22%), compared with 8.3% using the Wells score and the D-dimer testing.[69]

All of these AI models require a very large amount of high-quality data.[70] Further studies must be performed. This will require an international or even global sharing of anonymized data.

In the near future, we can easily imagine entering the characteristics and parameters of each patient and being guided by the algorithm to reliably suspect, exclude, or confirm PE.

Conclusion

For several decades, the clinical probability assessment has been the keystone of PE diagnostic strategy, mainly to exclude PE safely and with confidence. However, two incompletely met needs persist. The first of these is to rationalize testing for suspected PE to limit overtesting and overdiagnosis of PE. The second of these needs is that of achieving widespread implementation of accurate diagnostic management of suspected PE in current practice. Several innovations with these purposes are imminent and may profoundly change the diagnostic process for suspected PE in the near future.

Conflict of Interest
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