

APPLYING EVIDENCE TO THE DIAGNOSIS OF A PATIENT WITH SUSPECTED PULMONARY EMBOLISM: HOW TO USE AND EVALUATE A CLINICAL PREDICTION RULE

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In practice, we routinely rely on our clinical skills and experience to interpret findings on history, physical examination, and basic tests to arrive at a correct diagnosis for our patients. Making a diagnosis of pulmonary embolism (PE), however, is not so straightforward. Yet, it is critical for us to accurately identify patients with PE so appropriate therapy can be promptly administered, as untreated PE carries a high mortality risk. Similarly, we need to reliably rule out PE in those patients with other diagnoses to avoid potentially harmful interventions and unnecessary delay in administering needed treatments.

Fortunately, *clinical prediction rules* (CPRs)—also called *clinical decision rules*—are available to support our diagnostic evaluation of patients in whom we suspect PE. Based in the principles of evidence-based medicine (EBM), a CPR is defined as a tool that “quantifies the individual contributions that various components of the history, physical examination, and basic laboratory tests make toward the diagnosis, prognosis, or likely response to treatment in an individual patient” [1]. CPRs seek to increase the accuracy of our diagnostic and prognostic assessments and are useful when decision making is complex, the clinical stakes are high, or costs can be lowered without increasing risk to our patients [2].

This article uses a case of a patient with suspected PE to demonstrate the diagnostic value of a CPR in situations where uncertainty is high but accuracy is paramount. Understanding how to appraise the validity of these EBM tools is critical to the appropriate use of CPRs in practice. Although CPRs are not eas-

ily searched for in the literature and often require complex or cumbersome calculations, user-friendly computerized models are available on the Internet and search strategies have been devised to facilitate MEDLINE searching.

Assessing the Clinical Problem

You are a medical intern and your resident asks you to evaluate a patient just admitted from the outpatient practice. Mr. Williams is a 47-year-old man with worsening cough and left-sided pleuritic chest pain for the past 5 to 6 days. He has been a patient in the practice for 5 years. Your resident informs you that an electrocardiogram (ECG) was obtained while Mr. Williams was an outpatient, a chest radiograph was obtained on his way to the floor, and his blood work is pending. On your way to the floor, the nurse pages you to report that Mr. Williams’ oxygen (O₂) saturation is 89%. You ask her to start O₂ by nasal cannula at 2 L/min.

You find Mr. Williams sitting in a wheelchair beside his bed. He says he came to the outpatient practice today because he is worried about a cough and chest pain that have persisted despite a recent course of antibiotics. During the history you learn that Mr. Williams has emphysema and was hospitalized 1 month ago for shortness of breath. He was sent home on a prednisone “taper,” which he reports he took as directed. A few days after completing the prednisone he noticed a dry cough, which worsened over the next day. He went to a physician’s office near his apartment and was prescribed a course of antibiotics, which he took over 4 days. However, his cough did not improve and he developed chest pain. He points to his left lower chest and notes the pain is worse when he coughs and when he takes a deep breath. He also feels short of breath but denies fever, chills, or hemoptysis.

Mr. Williams has diabetes and underwent a left

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above-knee amputation (AKA) 3 years ago. He denies any pain or swelling in either lower extremity but reports having a blood clot in his right leg about 8 months ago, for which he took blood thinning medication for 6 months. He quit smoking around the time of his amputation. His current medications are a long-acting sulfonylurea, metformin, inhaled corticosteroids, ipratropium, and albuterol. Before you examine him, you ask him to transfer to his bed, which he does independently.

The patient appears older than his stated age. He has been speaking in full sentences and continues to cough intermittently. Vital signs are: blood pressure, 110/87 mm Hg; pulse, 110 bpm; respiratory rate, 22 breaths/min; and temperature, 37° C (98.6° F). Repeat O₂ saturation is 92%. Neck examination is negative for jugular venous distention at a 45° angle. The lungs are clear to percussion bilaterally, with mildly decreased breath sounds and scattered rhonchi throughout but no wheezing or rales. Cardiac examination reveals distant heart sounds but otherwise is unremarkable, with no audible gallops. Abdominal examination is normal except for scars consistent with past skin grafts. He has a left AKA, and there is no swelling or tenderness of his proximal left lower extremity or entire right lower extremity.

Mr. Williams' ECG shows sinus tachycardia, and his chest radiograph demonstrates a small infiltrate at the left costophrenic angle. Arterial blood gas results are: pH, 7.43; Pco₂, 49 mm Hg; Po₂, 79 mm Hg; and O₂ saturation, 88%. Complete blood count results are: white blood cell count, 13,100/μL (75% neutrophils, 23% lymphocytes); hemoglobin, 15.6 g/dL; hematocrit, 46%; and platelet count, 223,000/μL. Blood chemistries are normal. In the hospital information system you find results of previous radiologic studies for Mr. Williams. Right lower extremity ultrasound studies from 8 months ago show a thrombus in the midportion of the right superficial femoral vein. A chest radiograph from his last admission did not show an infiltrate.

You are increasingly concerned about PE in Mr. Williams, who presents with typical symptoms and risk factors for the diagnosis. You pause to weigh PE against other possible diagnoses before you call your resident and talk with your attending physician.

Managing Diagnostic Uncertainty

The diagnosis of PE is challenging and requires information beyond what is typically provided by the history, physical examination, and basic testing. It is easy to see why the intern in this case is concerned about

PE in Mr. Williams. Many features of Mr. Williams' presentation are consistent with a diagnosis of PE. However, PE presents with clinical signs and symptoms and findings on chest radiography, electrocardiography, and basic laboratory studies that may be ascribed to the presentation of many other medical conditions. In fact, evidence shows that most patients who present with a clinical picture similar to Mr. Williams' do not have PE [3]. If we are unfamiliar with the prevalence of PE in our practice population, we are likely to overestimate the probability that PE is present in our patients.

It is difficult to know how frequently the clinical features that Mr. Williams presents with are truly predictive of PE. How can we sort through clinical information to find the features that independently predict the presence of PE? As the case of Mr. Williams unfolds, we see how a CPR can help us to focus on the clinical features that have been shown to be accurate in predicting the probability of PE and that are helpful in managing diagnostic uncertainty in cases of suspected PE.

In thinking about a differential diagnosis, you review what you know about Mr. Williams. He has a history of chronic obstructive pulmonary disease and documented deep vein thrombosis (DVT) and presents with shortness of breath and pleuritic chest pain. He is afebrile but tachycardic. He is hypoxic with leukocytosis and has an abnormal chest radiograph. Since he completed a course of antibiotics before presenting to the practice and has been treated for DVT, you estimate that pneumonia is a less likely diagnosis than PE and that Mr. Williams is at high risk for PE. You decide that you should order a ventilation/perfusion (V/Q) scan and start heparin, and you page your resident to consult on the plan.

You summarize your clinical impressions for your resident, and she agrees with your plans to do a V/Q scan and to start anticoagulation. She adds that a D-dimer test also is useful for ruling out PE when combined with an assessment of the patient's probability of PE. She informs you that CPRs exist for PE and would be helpful in estimating pretest probability for PE in Mr. Williams. She says she will meet you to review the results of the V/Q scan with the radiologist and show you how to use the "Wells CPR."

Moments later your attending physician finds you at the nurses' station and asks about Mr. Williams. You present your findings thus far and say you estimate that Mr. Williams is at high risk for PE. When asked how you arrived at this estimate,

you explain your thinking, emphasizing Mr. Williams' history of DVT and recent antibiotic therapy. Based on the patient's new pulmonary infiltrate, your attending thinks a diagnosis of pneumonia is as likely as or more likely than PE. He therefore judges Mr. Williams' risk for PE as moderate. He agrees with your plan for a V/Q scan but does not think a D-dimer test will be useful since Mr. Williams' risk for PE is moderate, not low. Your attending does agree on the importance of using a CPR when making the diagnosis of PE and suggests that you familiarize yourself with one and present it at attending rounds later in the week.

Using a CPR to Estimate Pretest Probability

Based on individual clinical experience, different clinicians may place different values on the same set of clinical clues. Thus, to the extent possible, we should apply an evidence-based approach to estimating the probability of disease. By combining probabilities derived from the medical literature with the specific findings from our skillful examination of individual patients, we can minimize the potential for bias or other errors in our clinical judgment, thus making our pretest probability assessments more reliable. One valuable EBM tool to assist in this process is a CPR. A CPR is a rule derived and validated from clinical studies to predict outcomes for patients with specific clinical presentations. These rules rely on a predetermined set of clinical data points found to have predictive value, each with an assigned score.

Several such rules exist to predict the occurrence of PE, which combine specific symptoms, signs, and basic laboratory results into a pretest probability that a patient has PE. A CPR cannot diagnose PE but allows us to more reliably classify patients into low-, moderate-, or high-risk groups based on our initial clinical examination findings. Available evidence supports the use of CPRs for estimating probability of PE. In a recent systematic review of published studies using several different CPRs, the authors concluded that these tools are accurate and can be used by clinicians with all levels of experience; this review was published as part of the *JAMA* series, "The Rational Clinical Examination" [4]. Ideally, a CPR for PE should be used on the front line of patient care (ie, at the bedside).

The case of Mr. Williams is highly appropriate for the use of a CPR. Untreated PE has a high mortality rate. Thus, a correct diagnosis is critical, and the threshold should be low for including PE in our differential diagnosis. PE presents with a broad spec-

trum of symptoms and signs, making diagnostic testing beyond basic laboratory and radiologic studies a necessity. As clinicians, we will consider the diagnosis often, but based on the results of diagnostic tests and clinical follow-up will make the diagnosis infrequently. This was demonstrated in the well-known PIOPED (Prospective Investigation of Pulmonary Embolism Diagnosis) study, which used the gold standard of pulmonary angiography and/or 1-year follow-up to make the diagnosis of PE [3].

You find your resident in the nuclear medicine department. The radiologist calls you both into the reading room to review Mr. Williams' V/Q scan, which shows minimal blunting of the left costophrenic angle without significant mismatched segmental or subsegmental defects. The scan is interpreted as low probability for PE.

Back on the floor, your resident says she can quickly show you how to find and use the Wells CPR. Turning to a computer and using the *Google* search engine, she enters "clinical prediction rules." The second hit, "EBM HomePage," is the site she is seeking, which is an EBM site maintained by general internists at Mount Sinai School of Medicine. Clicking on the site and following the links, she quickly arrives at the CPR for PE, which is attributed to a 1998 study by Wells et al [5]. She hands the computer over to you to continue.

The site asks you to enter patient data in a stepwise fashion, which you do for Mr. Williams (**Figure 1A-E**). When asked whether there is an alternative diagnosis that is either "as likely or more likely than PE" or "less likely than PE," you first select "less likely," based on your assessment of the patient. The site then calculates the pretest probability of PE in Mr. Williams as 78.4% (69%–86%) or "high," with a post-test probability of 59% (47%–71%) after a low probability V/Q scan. Changing the alternative diagnosis of pneumonia to "as likely or more likely than PE," your attending physician's assessment, and recalculating lowers the pretest probability to 27.8% (23%–32%) or "moderate" and the post-test probability to 13% (11%–16%). You notice that recent antibiotic therapy does not factor into the rule. Mr. Williams' recent course of antibiotics was what led you to think pneumonia was less likely than PE and to estimate a high risk of PE. Seeing that this historical point has no predictive value, you are inclined to agree with your attending physician's moderate risk estimate.

When you later share the V/Q scan results with your attending, you acknowledge that the Wells CPR

A

Probability of Pulmonary Embolism
Return to EBM HomePage

Wells, PS, Ginsberg, JS, et al. (1998). "Use of a clinical model for safe management of patients with suspected pulmonary embolism." *Ann Intern Med* 129(12).

Important CPR Information

Rates of PE According to Pretest Probability

CPR Model used to Calculate Pretest Probability of PE

Respiratory Symptoms

Dyspnea or worsening of chronic dyspnea

Pleuritic chest pain

Chest pain that is nonretrosteral and nonpleuritic

Arterial oxygen saturation < 92% that corrects with oxygen supplementation < 40%

Hemoptysis

Pleural rub

NEXT

C

Risk Factors

Does the patient have any of the following risk factors?

Yes No

- Surgery within 12 weeks
- Immobilization (complete bedrest) for 3 or more days in the 4 weeks before presentation
- Previous DVT or PE
- Fracture of a lower extremity and immobilization of the fracture within 12 weeks
- Strong family history of DVT or PE (2 family members with known events or first-degree relative with hereditary thrombophilia)
- Cancer (treatment ongoing, within the past 6 months, or in palliative stages)
- Postpartum
- Lower extremity paralysis

BACK **NEXT**

B

Typical Features

Does the patient have any of the following? Yes No

- Heart rate greater than 90 bpm
- Leg symptoms
- Low-grade fever
- Chest radiograph consistent with PE

BACK **NEXT**

D

Severe Features

Does the patient have any of the following severe features?

Yes No

- Syncope
- Blood pressure less than 90 mm Hg with heart rate greater than 100 bpm
- Requires oxygen supplementation greater than 40%
- New onset right heart failure (elevated JVP an new S1, Q3, T3 or RBBB on ECG)

BACK **NEXT**

E

Calculate the Probability of PE

Is the alternative diagnosis (choose one):

As likely or more likely than PE

Less likely than PE

Click to calculate probability

Result of V/Q scan (choose one):

Normal

Low probability

Intermediate probability

High probability

Pretest probability of PE:
High: 78.4% (69%–86%)

Post-test probability of PE:
59% (47%–71%)

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Figure 1. Calculation of pretest and post-test probabilities of pulmonary embolism in case patient using the “extended Wells” clinical prediction rule. (Adapted with permission from Mount Sinai School of Medicine, Division of General Internal Medicine, Evidence-Based Medicine Web site [www.mssm.edu/medicine/general-medicine/ebm].)

suggests your earlier estimate of PE risk in Mr. Williams was too high. However, even with the low probability results of the V/Q scan, you both agree that the patient’s revised probability for PE is low at 13%, but not low enough to be certain that PE has been ruled out. Mr. Williams will need bilateral lower extremity compression ultrasonography.

Using a CPR to Guide the Diagnostic Approach
As the case of Mr. Williams unfolds, we see how it is possible for two physicians to generate different pre-

test probabilities when interpreting the same patient data. The intern’s initial assessment was that the patient was at high risk for PE, whereas the attending physician assessed risk as moderate. By using the Wells CPR for PE, the intern realizes that he had placed too much importance on the patient’s recent antibiotic therapy, which then allowed him to arrive at a pretest probability similar to the more experienced attending physician. This, in turn, helped guide a more accurate interpretation of Mr. Williams’ V/Q scan. Using the Wells CPR to interpret the

results of the low probability scan, the intern arrives at a post-test probability of 13%, similar to that of the attending physician. Clearly, CPRs offer significant value in supporting an evidence-based approach to diagnostic decision making in cases of PE by decreasing the variability in pretest probability estimates among providers with different levels of experience and leading to standardization of diagnostic strategies for PE.

Asking a Focused Clinical Question

Mr. Williams' ultrasound studies are negative for DVT. The team agrees that this finding probably lowers the patient's probability of PE to less than 13% but not low enough to rule out PE. Mr. Williams will need serial ultrasound studies and clinical follow-up to accurately assess his ongoing probability of PE. Repeat ultrasound studies are scheduled for 3 days later. Given the decreasing likelihood of PE, Mr. Williams is started on treatment for pneumonia and is switched to low-molecular-weight heparin for ease of administration.

Later that afternoon you ask your attending why he felt a D-dimer test would not have been helpful in this case. He says that while the evidence supporting use of this test is still emerging, it appears that the combination of a low pretest probability of PE on CPR and a normal D-dimer test is most reliable for ruling out PE and avoiding further tests. He adds that since Mr. Williams was at moderate risk, a D-dimer test would not have changed the diagnostic strategy. He recommends you read a recent systematic review of CPRs for PE from the "Rational Clinical Examination" series in *JAMA* [4] as part of your preparation for attending rounds.

The next day you begin preparing for your presentation and reflect on questions raised in the course of Mr. Williams' care. You wonder how the Wells CPR was developed and how accurate it is in predicting the likelihood of PE. You also want to know more about the evidence supporting use of a combination of CPRs and the D-dimer test in certain patients. You ponder how to translate these broad questions into focused queries to guide a search of the literature.

Before we search for evidence, we want to clarify our clinical questions, and the recommended approach to formulating an answerable question is to define PICO (patient, intervention, comparison, outcome) components. In most cases involving a diagnosis question, the value of this EBM step is clear. Focusing our clinical question helps to ensure that we efficient-

ly and effectively use evidence sources to find answers we need to make a diagnostic decision on behalf of our patient.

In the case of Mr. Williams, the attending physician suggested a PICO question and noted an important systematic review on the subject of CPRs, which should not be difficult to locate and may point us in the direction of individual studies we may wish to consult. Also, the Mount Sinai Web site provided information we need to locate the full text of the study on which the Wells CPR is based. This may be all the evidence we need.

It is useful to frame a diagnosis question to remind us of the EBM principles underlying such questions. For example, the outcome of interest typically is diagnostic accuracy and/or reliability, particularly in comparison to a gold standard, if one exists. In this case, the PICO components for a question about the combination of CPR and the D-dimer test might be defined as:

- P = hospitalized patient with suspected PE
- I = CPR for PE combined with D-dimer test
- C = definitive diagnostic workup
- O = accuracy of PE diagnosis

Using this framework, one question raised in the case of Mr. Williams is:

In a hospitalized patient with suspected PE, is the combination of a CPR for PE and a D-dimer test, compared with the results of a definitive diagnostic workup, reliable for accurately diagnosing PE?

Acquiring the Current Best Evidence

You frame a PICO question related to the combined use of a CPR and a D-dimer test for diagnosing PE but decide not to attempt a MEDLINE search just yet. Instead, you begin your evidence search by returning to the Mount Sinai EBM Web site where you found the Wells CPR. You find a citation for the 1998 study on which the CPR was based, by Wells et al [5], which was published in the *Annals of Internal Medicine*. You leave the site and click on your medical library's home page and open the link to the *Annals*. Searching on the date, author's name, and key words of the title, you quickly locate the article of interest. You download the full-text article and print it.

You then switch to the *JAMA* link on the library site and enter a search for "Rational Clinical Examination." The systematic review your attending suggested you read, by Chunilal et al [4], is the fourth article listed. You download and print it as well. The

title of the article piques your interest and you give it a fast read hoping to gain some perspective on the use of CPRs for diagnosing PE.

Skimming the abstract, you see that the authors advocate use of the CPRs they analyzed because of their accuracy in predicting the probability of PE when used by a variety of physicians. You learn that the Wells CPR you found on the Mount Sinai Web site is referred to as the "extended Wells model" and that this tool and the "simplified Wells model" were analyzed by the authors. You read that the simplified Wells model has been tested in three studies, and the title of one of these catches your eye because it includes some of the terms in your PICO question. The study, also by Wells et al [6], was published in the *Annals* in 2001. You locate this article on the journal's Web site, download it, and print it.

With two original studies of the Wells CPR and the systematic review of CPRs for PE, you feel have sufficient evidence to begin preparing for your presentation. You borrow a copy of the *Users' Guides to the Medical Literature* [7] from the resident library to acquaint yourself with criteria for appraising the evidence supporting use of a CPR.

Where and How to Find CPRs

We have seen how having a CPR on the front line of care is important. However, these tools are not easily searched for in the literature and often require complex calculations. If we consider CPRs as part of the standard evaluation of patients with suspected PE, as advocated by Chunilal et al [4], how can we readily find CPRs for PE?

Online resources. Collections of CPRs currently are accessible for free on at least three Internet sites. Each of these sites is easy to navigate. The Medical Algorithms Project Web site (www.medal.org) offers the most extensive collection—5100 algorithms organized into 45 major topics—and can be searched. The Wells model is found by clicking on the topic "Pulmonary & Acid Base" and scrolling down to the PE section. The CPR is formatted as an Excel document, which can be saved to a computer desktop, disk, or personal digital assistant. The site references the 1998 study by Wells et al [5] as the source of the CPR. The Mount Sinai EBM Web site (www.mssm.edu/medicine/general-medicine/ebm) lists 11 CPRs and appraises each rule based on the methodologic standards for rules that are at the derivation or validation stage of development. This site also provides the level of evidence that supports the use of each rule based on a hierarchy of evidence for CPRs. (The

methodologic standards for appraising a study validating a CPR and the levels of evidence for CPRs are detailed in the next section.) Finally, the Ottawa Health Research Institute Web site (www.ohri.ca/programs/clinical_epidemiology/OHDEC/clinical.asp) includes information on six CPRs.

MEDLINE search filter for CPRs. No medical subject heading (MeSH) terms for CPRs or clinical decision rules currently exist in MEDLINE. Thus, finding these EBM tools in the medical literature poses special challenges. Fortunately, Ingui and Rogers [8] published a study in which they derived and validated an optimal search filter to find CPRs in MEDLINE. They recommend the use of the filter "predict\$ OR clinical\$ OR outcome\$ OR risk\$," which retrieved 98% of CPRs in their validation study. Stated differently, this filter had a sensitivity of 98%, which means that 98% of studies about CPRs were retrieved. The authors used OVID to search MEDLINE. When using PubMed, the truncation symbol "\$" should be changed to "*".

Appraising Evidence for Validity and Importance

At home, you pull out the three articles you downloaded and the copy of the *Users' Guides to the Medical Literature* [7]. Consulting the *Users' Guides*, you learn that CPRs are first derived and then must be validated, with a final step being analysis of the rule's impact on clinical practice (**Figure 2**). You study the hierarchy of evidence for CPRs that should guide your appraisal of the evidence supporting the use of these tools in practice (**Table 1**).

Thinking about how to organize your presentation, you decide that you should first summarize what you have learned about CPRs from the *Users' Guides*, as this will provide an evidence-based context for evaluating a CPR. Then, you will apply the validation standards for a CPR (**Table 2**) to the 1998 extended Wells rule. After this, you will summarize the results of the 2001 study by Wells et al [6] that combines a CPR with D-dimer testing, which will answer your PICO question. Finally, you will use the systematic review [4] to determine where these rules fit in the hierarchy of evidence for CPRs (**Table 1**).

You begin your appraisal of the extended Wells model by consulting the standards for validation of a CPR (**Table 2**) and examining the 1998 study by Wells et al [5]. This study involved five Canadian medical centers and was designed to validate a CPR that the researchers had previously derived and tested in a pilot study. Consecutive inpatients and outpatients with suspected PE who had been symptomatic for

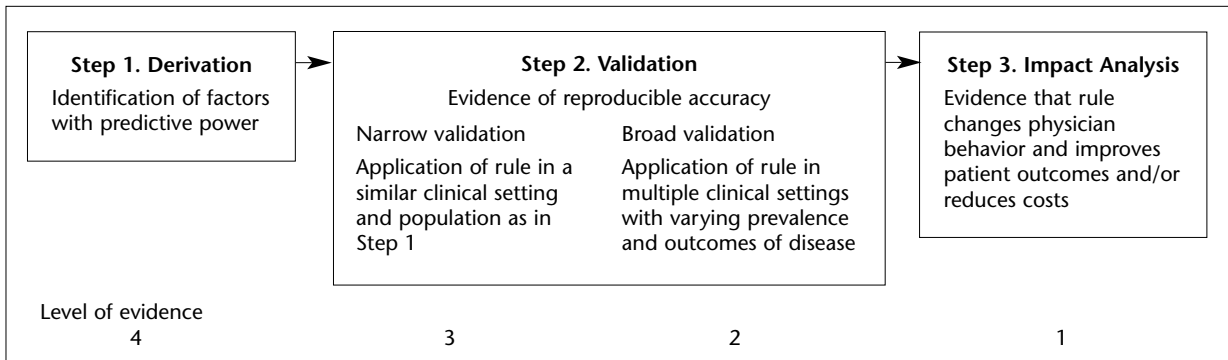


Figure 2. Development of a clinical prediction rule. (Adapted with permission from Guyatt G, Rennie D. *Users' guides to the medical literature*. Chicago: AMA Press; 2002:474. Copyright © 2002, American Medical Association. All rights reserved.)

less than 30 days were eligible. A total of 1885 patients were initially evaluated; 484 were not eligible to participate, and results from 1239 patients were analyzed. The reasons for ineligibility for all 484 patients were explicitly detailed, with 33% (152/484) excluded because of prolonged anticoagulant therapy. The radiologists who interpreted the V/Q scans had no knowledge of the results obtained by the physicians using the CPR, which was applied to each patient before the V/Q scan was performed. All patients were followed for 3 months after enrollment. Satisfied that this study meets the methodologic standards for validation of a CPR, you examine the results. The CPR accurately placed patients into low (3.4% [CI, 2.2% to 5%], intermediate (28% [CI, 23.4% to 32.2%]) or high (78% [CI, 69.2% to 89.6%]) categories for the probability of PE, with a statistically significant different prevalence of PE among the categories.

Next, you turn your attention to the 2001 study by Wells et al [6]. This study used a simplified CPR (Table 3) derived from data collected on the 1239 patients in the 1998 study [5] combined with D-dimer testing to estimate the probability of PE. A total of 946 consecutive patients presenting at four Canadian emergency departments were enrolled. After the simplified Wells CPR model was applied, D-dimer testing was performed. You are satisfied that this study also meets the criteria for validation of a CPR and turn to the results, which are similar to the first study. The CPR placed patients into low (1.3% [CI, 0.5% to 2.7%]), moderate (16.2% [CI, 12.3% to 20.6%]), and high (40.6% [CI, 28.7% to 53.7%]) probability groups, with a statistically significant difference in the prevalence of PE among the groups. Patients with a low probability for PE and a negative D-dimer test had no further diagnostic testing and were then fol-

Table 1. Hierarchy of Evidence for Clinical Prediction Rules

Level 1: Rules that can be used in a wide variety of settings with confidence that they can change clinician behavior and improve patient outcomes

At least 1 prospective validation in a different population and 1 impact analysis, demonstrating change in clinician behavior with beneficial consequences

Level 2: Rules that can be used in various settings with confidence in their accuracy

Demonstrated accuracy in either 1 large prospective study including a broad spectrum of patients and clinicians or validated in several smaller settings that differ from one another

Level 3: Rules that clinicians may consider using with caution and only if patients in the study are similar to those in the clinician's clinical setting

Validated in only 1 narrow prospective sample

Level 4: Rules that need further evaluation before they can be applied clinically

Derived but not validated or validated only in split samples, large retrospective databases, or by statistical techniques

Adapted with permission from Mount Sinai School of Medicine, Division of General Internal Medicine, Evidence-Based Medicine Web site (www.mssm.edu/medicine/general-medicine/ebm).

lowed for 3 months. The follow-up for this patient group was the reference standard used to determine the accuracy of the diagnostic strategy combining the simplified Wells CPR with D-dimer testing. Only 1 patient of 427 with a low probability for PE and a negative D-dimer test developed PE during the 3-month follow-up period.

You next turn to the systematic review by

Table 2. Methodologic Standards for Validation of a Clinical Prediction Rule

1. Were the patients chosen in an unbiased fashion and do they represent a wide spectrum of severity of disease?
2. Was there a blinded assessment of the criterion standard for all patients?
3. Was there an explicit and accurate interpretation of the predictor variables and the actual rule without knowledge of the outcome?
4. Was there 100% follow-up of those enrolled?

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Chunilal et al [4], which will help you determine where the extended and simplified Wells rules fit into the hierarchy of evidence for CPRs. You find that the extended Wells rule has been validated in two additional studies [9,10], with a total of 505 patients. The systematic review also describes two studies that prospectively evaluated the simplified Wells CPR [9,11], with a total of 691 patients. These prospective validation studies elevate both the extended and simplified versions of the Wells CPR to level 2 in the CPR evidence hierarchy.

Referring to the schema for the development of a CPR and the hierarchy of evidence, you see that to reach level 1 requires an impact analysis demonstrating a beneficial change in physician behavior. Since none of the studies in the systematic review is an impact study, the extended and simplified Wells CPRs are definitely level 2 CPRs. Finally, even though the two studies by Wells et al [5,6] are not impact studies, you find that both did show decreased use of resources without significantly compromising patient safety.

CPR Validation and Hierarchy of Evidence

After locating a CPR, we first need to distinguish between CPRs that have been derived but not validated and those that have been validated. Validation is an essential step before we should consider using a CPR in clinical practice; only rules that have been validated in predicting the diagnosis of interest should be used. The next step is to determine where the CPR fits in the hierarchy of evidence for CPRs. To help clinicians determine which CPRs are appropriate for patient care, the authors advocate that online resources for CPRs and published validation studies be explicit in the level of evidence supporting a CPR.

Table 3. The Simplified Wells Scoring System

Findings	Score*
Clinical signs/symptoms of deep venous thrombosis (minimum of leg swelling and pain with palpation of the deep veins of the leg)	3.0
No alternate diagnosis likely or more likely than pulmonary embolism	3.0
Heart rate > 100 bpm	1.5
Immobilization or surgery in last 4 weeks	1.5
Previous history of deep venous thrombosis or pulmonary embolism	1.5
Hemoptysis	1.0
Cancer actively treated within last 6 months	1.0

Adapted with permission from Wells PS, Anderson DR, Rodger M, et al. Derivation of a simple clinical model to categorize patients with probability of pulmonary embolism: increasing the models utility with the SimpliRED D-dimer. *Thromb Haemost* 2000;83:416–20.

*Category scores are as follows: low, < 2; moderate, 2–6; and high, > 6. Patient's clinical score is calculated by the summing of the scores (weight) of the predictor variables that are present.

Using the criteria for assessing the validity of a CPR (Table 3), we see that the extended and simplified Wells CPRs have been validated in different studies and at different sites. These studies advance both rules to level 2 in the CPR evidence hierarchy. However, neither the extended nor the simple Wells model meets criteria for level 1 evidence, as there has not been an impact study that demonstrates a beneficial change in physician behavior (eg, decreased test ordering) and improved patient outcomes (eg, a decrease in the number of missed diagnoses).

Applying Evidence to Patient Care

On hospital day 4, Mr. Williams undergoes another round of bilateral lower extremity ultrasound studies, which again are normal. He is improving, and it is determined that he can be discharged home on a regimen of antibiotics and low-molecular-weight heparin until he has completed the requisite serial ultrasound studies.

Later that afternoon, you reflect on where Mr. Williams fit into the clinical scenarios from the two studies you appraised. In the first study by Wells et al [5], 403 patients were assessed at moderate risk for PE. Including PE diagnosed at the time of enrollment and in the 3 months of follow-up, 112 of these patients (27.8%) were ultimately diagnosed with PE.

Looking closer at patients like Mr. Williams, 248 patients assessed at moderate pretest probability had non-high probability V/Q scans and, of these, 19 had initially abnormal ultrasound studies and 7 had abnormal ultrasound results on serial testing. The authors report that normal serial ultrasonography has a negative predictive value of 99.5%. As for the 2001 study by Wells et al [6], since Mr. Williams did not present at low risk for PE, you now understand why your attending physician did not emphasize a D-dimer test in the diagnostic strategy. If a D-dimer test had been ordered, regardless of the results, Mr. Williams still would have undergone V/Q scanning and serial ultrasounds because he was at moderate risk.

Based on your appraisal of the evidence, you are convinced of the value of CPRs in the diagnosis of PE, and in the future, you will use a CPR when assessing the probability of PE in your patients. You are now ready to present the steps in the development of a CPR and your appraisal of the 1998 Wells CPR [5]. You will summarize the 2001 study by Wells et al [6], emphasizing the value of a D-dimer test in patients who present with a low probability for PE. Finally, you will present the level of evidence for both CPRs based on where they fit in the hierarchy of evidence.

The application of a CPR to patient care should be guided by the level of evidence supporting the rule. Because the extended Wells CPR is supported by level 2 evidence, it was appropriate to use in this case of suspected PE.

As seen in the case of Mr. Williams, CPRs are particularly useful when interpreting the results of initial diagnostic testing. They also can guide us when ordering and interpreting further tests that may be necessary to confirm a diagnosis and can inform us when a diagnostic test will not be useful, as was the case of D-dimer testing for Mr. Williams. By avoiding exposure to unnecessary tests, CPRs may reduce costs and, importantly, may decrease risk to patients. Finally, CPRs may guide therapeutic decisions, such as the decision to continue low-molecular-weight heparin in Mr. Williams until his serial ultrasound studies are completed—a decision supported by the extended Wells CPR.

Conclusion

Table 4 summarizes the five-step EBM approach as it applies to the evaluation of Mr. Williams for PE. In this case, we have demonstrated the accuracy of CPRs in predicting the outcome of diagnostic testing in patients with suspected PE. We also have seen how

Table 4. Summary of the Evidence-Based Medicine Approach to Making a Diagnosis of PE in Mr. Williams

Assess	
The patient	Mr. Williams is admitted with shortness of breath, cough, and pleuritic chest pain. His history is positive for treated DVT and a recent exacerbation of COPD requiring steroids, followed by oral antibiotics as an outpatient. He has a small infiltrate at the left costophrenic angle.
The problem	Intern suspects PE but cannot definitely diagnose PE based on findings on history, physical examination, basic laboratory tests, chest radiograph, and ECG. Further testing is necessary. Intern estimates high probability for PE in Mr. Williams and suggests V/Q scan plus D-dimer testing. Attending physician estimates moderate probability for PE and suggests V/Q scan but no D-dimer testing.
Ask	
	In a hospitalized patient with suspected PE, is the combination of a CPR for PE and a D-dimer test, compared with the results of a definitive diagnostic workup, reliable for accurately diagnosing PE?
Acquire	
	Two studies of the Wells CPR for PE and one systematic review of CPRs for PE.
Appraise	
	The extended and simplified Wells CPRs for PE meet the methodological standards for validation studies. Both rules are level 2 in the hierarchy of evidence for CPRs.
Apply	
	For patients who present similarly to Mr. Williams, using a CPR can guide the interpretation of test results and avoid more invasive testing. In patients with low probability for PE based on a CPR, a negative D-dimer test accurately rules out PE.

COPD = chronic obstructive pulmonary disease; CPR = clinical prediction rule; DVT = deep vein thrombosis; ECG = electrocardiogram; PE = pulmonary embolism; V/Q = ventilation/perfusion.

important it is for senior residents and attending physicians to introduce and recommend the use of CPRs for PE to the trainees whom they supervise.

For PE, the accuracy of CPRs has led to their recommended use in all patients with suspected PE. As studies proliferate that derive and validate CPRs,

EBM has given us the tools to assess new CPRs and their place in the hierarchy of evidence for CPRs. Ideally, all CPR studies should be explicit in identifying the level of evidence supporting a CPR.

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