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1 Pulmonary Embolism Diagnosis: 2 Clinical assessment at the front 3 door

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10

11 Abstract

12 This first of two practice reviews addresses PE diagnosis considering important aspects of PE
13 clinical presentation and comparing evidence-based PE testing strategies. A companion paper
14 addresses the management of PE [1]. Symptoms and signs of pulmonary embolism (PE) are
15 varied, and emergency physicians frequently use testing to ‘rule out’ the diagnosis in people
16 with respiratory or cardiovascular symptoms. The emergency clinician must balance the benefit
17 of reassuring negative PE testing with the risks of iatrogenic harms from over investigation and
18 overdiagnosis.

19 Manuscript text

20 INTRODUCTION

21 Pulmonary embolism (PE) occurs when a thrombus, usually originating in the deep veins of
22 the lower limbs or pelvis, lodges in the pulmonary arteries. Without early treatment, PE can
23 progress to become fatal [2,3]. The clinical diagnosis of PE remains challenging; ‘classical’
24 symptoms such as dyspnoea and chest pain are not always present in the context of acute
25 disease, and features such as haemoptysis, unilateral extremity swelling and syncope are even
26 less frequent [4]. There are no reliable discriminating features that individually confirm or
27 exclude disease [5]. However, the consequences of missed disease can be serious; in a case
28 series of in-hospital autopsy cases with pathological findings of PE, in only one third of cases
29 was the diagnosis of PE considered antemortem [6]. As a result, clinicians considering the
30 diagnosis of PE increasingly rely on objective laboratory and radiological investigation.

31

32 Computed tomography pulmonary angiography (CTPA) is the current imaging modality of
33 choice in the context of suspected PE. This strategy is costly, time consuming, incurs
34 potentially unnecessary irradiation and often detects incidental findings requiring further
35 investigation [7]. In addition, indiscriminate use can lead to misdiagnosis of PE and potential
36 overuse of therapeutic anticoagulation [8].

37

38 It is vital that clinicians have a pragmatic and evidence-based understanding of these challenges
39 to enable provision of optimal care for patients. This practice review explores how a diagnosis
40 of PE might be made and contextualises evidence-based diagnostic strategies.

41

42 CLINICAL PRESENTATION

43 Which clinical factors are risks for PE?

44 A meta-analysis of diagnostic studies in 2007 reported that in the context of clinical suspicion,
45 past history of venous thromboembolism (VTE), active cancer, immobilization, exogenous
46 oestrogen and recent surgery are independent predictors of PE diagnosis [5]. Cancer is a key
47 VTE risk factor for multiple reasons: it often leads to a pro-coagulant state; cancer patients
48 have frequent hospitalizations and surgeries; indwelling venous catheters are common; and
49 some cancer treatments directly promote thrombus formation [9]. People with a first degree
50 family history of venous thrombosis have a two to four fold higher odds of developing venous
51 thrombosis themselves, independent of known thrombophilia [10]. These individual risks are
52 cumulative [11]. For example, a person with a prior history of VTE has an increased risk of a
53 recurrent thrombotic event, however if they are subsequently diagnosed with cancer and then
54 undergo surgery, their personal risk of VTE will continue to increase with each additional risk
55 factor.

56

57 Symptoms and signs

58 The presence of dyspnoea, haemoptysis, syncope and leg swelling all individually increase the
59 likelihood of PE diagnosis [5]. Symptoms of deep vein thrombosis have been reported in 23%
60 of confirmed PE cases [12]. The most commonly reported symptoms of PE are shortness of
61 breath (likelihood ratio (LR) of 1.4 (95% confidence interval (CI) 1.1-1.8)) and chest pain (LR
62 1.1 (95% CI 0.8-1.3)) [4,5]. 'Classic' pleuritic chest pain has been found to occur as frequently
63 as in 39.4% of patients with confirmed PE. A large embolic burden can also present with pre-
64 syncope or syncope (LR 2.4 (95% CI 1.5-3.7)) on exertion [5].

65

66 Clinical findings on examination also vary in prevalence. Theoretically, the larger the embolic
67 burden, the more likely there are to be signs of cardiovascular compromise, such as clinical
68 shock (LR 4.1 (95% CI 1.8-8.9)) [5,13]. Absence of tachypnoea reduces the likelihood of PE
69 (LR 0.6, (95% CI 0.4-0.8)) [5].

70

71 Electrocardiography (ECG)

72 ECG findings are never diagnostic for PE, and patients with acute disease will frequently have
73 sinus rhythm with a normal heart rate [14]. However, the ECG is vital to assess the likelihood
74 of important differentials, such as acute myocardial infarction, particularly in the context of

75 ongoing chest pain. Inverted T-waves in leads III and V₁ can be seen in acute PE and are rare
76 in acute coronary syndrome [15]. The most common ECG findings in PE are sinus tachycardia,
77 non-specific ST segment changes and T-wave changes [16]. The classic finding of an S wave
78 in lead I, a Q wave and inverted T-wave in III, (S1Q3T3) has been previously reported as 97%
79 specific for right ventricular enlargement in the context of confirmed PE, although sensitivity
80 is poor at 7.1% [17]. Signs of right ventricular strain on ECG can be potentially predictive for
81 clinical deterioration in the context of confirmed PE, but add little to the diagnostic process
82 [18].

83

84 **Chest radiography**

85 The chest x-ray (CXR) is a routine investigation for any patient presenting to the emergency
86 department (ED) with chest pain and/or breathlessness. In the context of suspected PE, CXR
87 can help exclude alternative diagnoses (e.g. pneumothorax, pneumonia) and may aid diagnosis
88 of rare pathology (e.g. aortic dissection, pericardial effusion). In addition, there are subtle signs
89 on CXR which can potentially increase the clinical concern for PE, including the Westermark
90 sign (oligaemia), Fleischner sign (prominent central pulmonary artery) and Hampton hump
91 (pleural-based area of increased opacity). When studied in isolation, all are poor predictors of
92 PE diagnosis [19]. A normal CXR is not sensitive for ruling out PE, with a prospective
93 observational study finding 40.1% of patients ultimately diagnosed with PE having no
94 abnormal CXR findings [4]. A CXR suggestive of alternative diagnosis is also not sensitive for
95 ruling out PE, with atelectasis (16.9%), effusion (16.2%) and infiltrates (13.5%) being
96 concurrent in patients ultimately diagnosed with PE [4]. Similar data has also been reported in
97 the PE in pregnancy literature, with the DiPEP study reporting CXR abnormalities (both PE-
98 related and PE-unrelated) in patients with and without embolic disease [20]. Clinicians should
99 therefore be cautious in attributing non-specific CXR findings to alternative, non-PE
100 diagnoses.

101

102 **HOW TO TEST FOR PE**

103 **When should you test for PE?**

104 The decision to evaluate for PE is dependent on compatible clinical presentation, assessment
105 of risk factors and clinician gestalt. The presence of established VTE risk factors should
106 influence pretest probability and increase suspicion in the context of less specific symptoms.

107 Clinicians should also consider testing for PE in patients with unexplained breathlessness,
108 especially when exertional breathlessness is poorly explained by other diagnoses.

109

110 When PE is raised as a differential diagnosis in the ED, it is common for clinicians to approach
111 the consultation wanting to ‘rule out’ PE as a diagnosis. However, this is trickier than it seems.
112 Even pulmonary angiography, widely regarded as the reference standard investigation, has a
113 reported 90-day VTE diagnosis rate following negative testing of 1.1% (95% CI 0.5-2.2%)
114 [21]. A pragmatic approach is to avoid imaging when the pretest probability of PE is so low
115 that further diagnostic imaging would be as likely or more likely to cause harm than to provide
116 benefit [22]. Consequently, patients with negative testing for acute PE should always be
117 advised to seek further medical review if their symptoms worsen. In addition, patients with
118 negative tests for acute PE may be experiencing symptoms from another aetiology, which
119 requires further investigation and treatment.

120

121 **Deciding whether to test for PE**

122 The pulmonary embolism rule-out criteria (PERC) [Table 1] contains 8 specific
123 demographic/clinical features and is designed for use in patients where the diagnosis of PE is
124 being considered but is felt to be unlikely. Prior studies have classified an unlikely gestalt
125 further, at a pretest probability of PE estimated to be less than 15% [23]. If all PERC criteria
126 are negative, the probability of harm from CT scanning is likely to be greater than the benefit,
127 supporting cessation of further work up for PE. PERC is now highlighted within guidance
128 produced by the National Institute for Health and Care Excellence, European Society of
129 Cardiology and American College of Emergency Physicians. It has also been advocated within
130 the North American ‘Choosing Wisely’ campaign to reduce unnecessary diagnostic testing in
131 emergency medicine [24–27]. PERC allows a safe, rapid, and convenient assessment for
132 patients without the need for invasive tests. However, concerns remain about how to define
133 patients suitable for evaluation using PERC. A large cluster randomised trial included patients
134 who the treating clinician estimated the pretest probability to be less than 15% [28]. In this
135 study, the true pretest probability was only 2%, suggesting that clinicians over-estimated the
136 pretest probability of PE. The implications of applying PERC to a population where PE is not
137 really suspected or where clinicians over-estimate the pre-test probability of PE, is that it is
138 likely to lead to an increase in unnecessary testing in those who are PERC positive (e.g. over
139 50) without any real clinician suspicion of PE. In attempt to reduce subjectivity, some authors

140 have studied application of the PERC rule to low probability patients identified through prior
 141 structured pretest probability assessment using the Wells or revised Geneva scores [29,30].
 142 This approach has potential advantages and a developing evidence base, but no supporting
 143 randomised trial data. There is no evidence base yet to support the application of the PERC
 144 rule after YEARS assessment in YEARS negative patients, and if using a YEARS based
 145 strategy, PERC should be applied before YEARS assessment/D-dimer testing.

146

147 **Table 1:** Overview of the PE Rule Out Criteria (PERC) clinical decision rule

When to use	Following history and examination where PE is thought to be unlikely (i.e. pretest probability is < 15%)	
Criteria	<ul style="list-style-type: none"> • 50 years of age or older • Heart rate 100 or more • SpO2 on room air less than 95% • Unilateral leg swelling • Haemoptysis • Surgery requiring general anaesthesia or trauma within the past 4 weeks • Prior PE or DVT • Any hormone use 	
Interpretation	If the test is negative (i.e. no items are present): investigation of PE is unlikely to benefit the patient and can be stopped. Estimated incidence in this group is 0.9% [23]	If the score is positive (i.e. any items are present): PE cannot be excluded clinically and further work up would be required in order to reject the diagnosis.

148 *Adapted from [23].*

149

150 **Clinical probability estimation**

151 Tacit knowledge and clinical gestalt are often useful in complex clinical medicine. However,
 152 this approach can be unsatisfactory for reliable and reproducible PE testing because of the
 153 unavoidable risk of bias and the overestimation of pretest probability [31]. A more structured
 154 estimate for the probability of PE is provided by clinical models, several of which have been
 155 derived and validated in large populations of emergency patients. It is worth noting that Wells
 156 and YEARS do still incorporate clinical gestalt to some degree (e.g. pulmonary embolism the
 157 most likely diagnosis in YEARS and alternative diagnosis less likely than PE in Wells) and
 158 clinical gestalt may be used to determine when to apply and how to interpret structured models.
 159 In addition, when structured models have been compared against clinical gestalt alone in
 160 observational cohort studies, there appears to be little difference in diagnostic accuracy [32].
 161 The optimal approach is therefore likely to be a structured estimate alongside clinical gestalt,
 162 rather than a structured estimate alone. **Table 2** summarises the most common validated
 163 structured pretest probability assessments in clinical use at present, their components and
 164 associated stratification.

165

166 **Table 2:** Comparison of validated structured pretest probability assessments for PE diagnosis

Tool	When to employ	Variables (score)	Outcome (PE prevalence)
Wells PE [33]	Applicable for all patients following history and examination where PE is suspected	Clinical signs of DVT (3) Alternative diagnosis less likely than PE (3) Previous PE or DVT (1.5) Heart rate >100 (1.5) Surgery or immobilisation within the past 4 weeks (1.5) Haemoptysis (1) Active cancer (1)	Two level score: 0-4 PE unlikely (8.4%) 4.5 or more PE likely (34.4%)[34] Three level score: Low (5.7%) Intermediate (23.3%) High (49.3%) [34]
Simplified Revised Geneva [35]	Following history and examination where PE is suspected	Previous PE or DVT (1) Heart rate 75-94bpm (1) Heart rate 95bpm or greater (1) Surgery or fracture within past month (1) Haemoptysis (1) Active cancer (1) Unilateral lower limb pain (1) Pain on lower limb deep venous palpation and oedema (1) Age greater than 65 (1)	0-1 Low risk (7.7%) 2-4 Intermediate risk (29.3%) 5 or more High risk (64.3%)[34]
YEARS [36]	Following history and examination where PE is suspected, a YEARS score is done and a D-dimer taken.	<i>YEARS items:</i> Clinical signs of deep vein thrombosis Haemoptysis Pulmonary embolism the most likely diagnosis	No YEARS items and D-dimer <1000 ng/ml (0.3%) No YEARS items and D-dimer ≥1000 ng/ml (14.4%) Any YEARS item and D-dimer <500 ng/ml (0.9%) Any YEARS item and D-dimer ≥500 ng/ml (29.2%)

167 *DVT: deep venous thrombosis; PE: pulmonary embolism. Note that prevalence of PE in YEARS*
 168 *row is not directly comparable to the two other scores because the presence or absence of*
 169 *variables necessarily affects investigation strategy.*

170

171 The Wells PE or Geneva scores (see **Table 2**) are used to identify patients who have a lower
 172 probability of having PE. Patients with a lower probability of PE (Wells unlikely or Geneva
 173 low/moderate) can progress to further evaluation with D-dimer testing, in attempt to reduce the
 174 potential harm associated with imaging studies [37,38]. These clinical models have advantages
 175 and disadvantages. For example, the Wells PE has the fewest items to remember and the
 176 commonly used two level outcome score simplifies interpretation. However, Wells contains
 177 points for clinician gestalt (i.e. PE is the most likely diagnosis), raising concerns about
 178 reproducibility of the score, with reported poor interobserver reliability [39]. Both the Wells
 179 and Geneva scores have been extensively validated, and prospective efforts to compare the two
 180 approaches have not demonstrated superiority of either method [40,41].

181

182 **D-dimer thresholds**

183 In acute PE, activation of the coagulation and fibrinolysis pathway leads to elevation in blood
 184 D-dimer levels. Although the D-dimer result is a continuous variable, it is often reported with
 185 a prespecified manufacturer recommended dichotomous cut off (usually <500 ng/mL FEU). In
 186 this context, a negative test is routinely used to exclude PE in patients with a low to moderate
 187 probability, given the high negative predictive value of D-dimer [42]. There is evidence that
 188 adjusting the D-Dimer cut off by age can also safely exclude PE in patients with a Wells
 189 unlikely, or Geneva low / moderate score [37]. This approach carries the advantage of
 190 improved specificity (further reducing the need for imaging and the associated harms) without
 191 any decrease in sensitivity. There is also increasing evidence that adjusting the D-dimer cut off
 192 based on initial clinical probability estimation is more efficient than other methods. The
 193 YEARS algorithm [36] varies the D-dimer cut off based on the presence of YEARS items
 194 (clinical signs of DVT; haemoptysis; PE being the most likely diagnosis). The PEGeD study
 195 used clinical probability-adjusted D-dimer cut offs based on estimation using the Wells score;
 196 this approach has only been validated in one prospective study to date [43]. The range of
 197 approaches is compared in **Table 3**.

198

199 **Table 3:** Comparison of D-dimer cutoff approaches

	Standard approach	Age adjusted D-dimer	Clinical probability adjusted D-dimer	YEARS
Method	PE ruled out if D-dimer <500 ng/mL* when combined with low-moderate clinical probability	PE ruled out if D-dimer < (10 x age of patient) (if age >50) when combined with low-moderate clinical probability	When Wells PE score <4.0, PE ruled out with D-dimer <1000 ng/mL When Wells PE score 4.5 – 6.0, PE ruled out with D-dimer <500 ng/mL	When no points scored for YEARS, PE ruled out with D-dimer <1000 ng/mL Otherwise, PE ruled out with D-dimer <500 ng/mL
Potential benefits	Simple, already embedded into most local protocols, compatible with straightforward auto-alerts on electronic laboratory report systems	Addresses increasing D-dimer with age, reduces imaging in older population	Incorporates pre-test probability into D-dimer interpretation, reduces imaging in low-risk presentations	Simpler than clinical probability adjusted D-dimer, reduces imaging in low-risk presentations
Validation	Very extensively validated in multiple independent prospective cohort studies.	Validated in many post hoc analyses of prospective diagnostic PE studies outside of index cohort study [44]	Validated in one prospective cohort [43]	Formally validated in two prospective studies by post hoc analysis, outside of index cohort [45,46]
What proportion of patients would undergo CTPA?	59.8% of patients required chest imaging [43]	43.9% of patients required chest imaging [43]	35.1% of patients required chest imaging in original PEGeD study [43]	36.3% of patients required chest imaging [43]
Reported VTE event rate at 3 months when anticoagulation withheld using	0.1% (95% CI 0.0 to 0.7) [47]	0.3% (95% CI 0.1 to 1.7) [47]	0.0% (95% CI 0.0 to 0.3) [43]	0.61% (95% CI 0.4 to 1.0) [36]

this diagnostic strategy				
--------------------------	--	--	--	--

200 CTPA: computer tomography pulmonary angiogram; PE: pulmonary embolism. * When using
 201 a D-dimer assay with a manufacturer recommended cutoff of 500 ng/ml

202 IMAGING

203 CTPA is the most frequently used and most widely available imaging modality for PE
 204 diagnosis. However, other options remain available in most healthcare systems. There are
 205 several important considerations; pretest probability, timing, contraindications and whether
 206 alternative imaging strategies may be more appropriate. The relative merits of imaging
 207 modalities are summarised in **Table 4**.

208

209 **Table 4:** Relative strengths and weaknesses of imaging modalities for PE.

Modality	Strengths	Disadvantages
CTPA	Widely available including out of hours Relatively fast procedure May provide alternative diagnosis Low rate of inconclusive results (3-5%)	Risk of anaphylaxis to contrast/iodine Risk of contrast nephropathy Radiation dose: 3-10mSv, a particular risk for young and pregnant women because of breast tissue irradiation
Planar V/Q	Almost no contraindications Well validated[48] Lower radiation dose	Relatively poor availability, only available in day hours. Must combine result with previously documented clinical probability to rule in or rule out PE Inconclusive in up to 50% of cases Higher radiation dose for foetus compared to CT in pregnant patients Radiation dose ~2mSv
V/Q SPECT	Almost no contraindications Binary answer	Not extensively validated Variability in method and nonstandard diagnostic criteria Radiation dose ~2mSv

210 CTPA: Computed Tomography Pulmonary Angiography; SPECT: single photon emission
 211 computed tomography; V/Q: ventilation/perfusion.

212

213 CTPA is usually first choice imaging, with relative ease of access in many EDs. Advances in
 214 technology (e.g. dual source CT) are leading to higher imaging quality and a relative reduction
 215 in ionising radiation/contrast dose requirements, improving safety for patients [49]. However,
 216 there is increasing concern about false positive PE diagnoses, with easier detection of smaller
 217 (subsegmental) clots and ensuing questions on clinical relevance / need for treatment [50].

218

219 Planar V/Q (ventilation/perfusion) imaging provides an established alternative to CTPA.
 220 However, definitive results are less likely when there is an abnormal chest x-ray and unlike
 221 CTPA, this strategy rarely provides an alternative diagnosis. To diagnose or exclude PE, the
 222 planar V/Q result must match patient clinical probability. [25] Unlike planar V/Q, V/Q SPECT

223 provides a binary result ('PE' versus 'no PE'). However, whilst a recent meta-analysis
224 suggested V/Q SPECT may have high sensitivity and high specificity for the diagnosis of PE,
225 [51] there remain issues in the variability of technique and diagnostic criteria as well as the
226 lack of validation through prospective management outcome studies. The technique is also not
227 widely available and consigned to daylight hours.

228

229 Compression ultrasound (CUS) has a sensitivity >90% and a specificity of ~95% for proximal
230 symptomatic deep vein thrombosis (DVT), and confirmation of DVT can sometimes negate
231 the need for further pulmonary imaging to confirm VTE in haemodynamically stable patients
232 [52]. Although out of hours availability is often limited, it remains a useful diagnostic option
233 to rule in DVT (and presume a diagnosis of PE) in a patient with suspected PE and relative
234 contraindications to CTPA.

235

236 Point of care ultrasound (POCUS) is an additional assessment tool for trained emergency
237 clinicians and can impact pre-test probability. The sensitivity of POCUS for DVT appears to
238 be reasonable when compared to formal sonographer CUS evaluation [53,54], although it
239 remains operator dependent. POCUS may be useful to rule in DVT (and increase pre-test
240 probability of PE) in a patient with suspected PE who is unstable or has relative
241 contraindications to CTPA. POCUS can also be used to assess for indirect signs of PE,
242 including right ventricular dilation, abnormal tricuspid annular plan systolic excursion
243 (TAPSE), McConnell's sign and increased pulmonary artery pressure [55]. All demonstrate
244 good correlation with severity in the context of confirmed PE, although TAPSE has the highest
245 sensitivity and specificity for early mortality [56]. POCUS may have a particular role in
246 evaluating patients during cardiopulmonary resuscitation, given ease of access, the potential to
247 influence treatment modalities and widespread availability [57].

248

249 Magnetic Resonance Pulmonary Angiography (MRPA) with gadolinium contrast is an
250 alternative imaging modality, with sensitivities ranging from 31-92% and specificities quoted
251 between 85-100% [58]. However, there are concerns about acceptability to patients, access is
252 often limited from the ED, and the method is contraindicated in pregnancy and renal failure
253 because of the contrast agent. Without contrast, sensitivity has been estimated as low as 82%
254 compared to CTPA [59].

255

256 THE PREGNANT PATIENT

257 In the western world, PE is a leading (albeit rare) cause of mortality in pregnant patients [60].
258 Diagnosis can be challenging as many PE symptoms also result from normal physiological
259 changes associated with pregnancy. Imaging is a source of unease as methods often require
260 radiation exposure for mother and foetus. Pregnant patients have been excluded from most
261 diagnostic PE research, so there is a relative lack of evidence to guide testing [61].

262

263 A recent prospective cohort study reported a pregnancy-adapted YEARS protocol utilising D-
264 dimer to safely rule out PE across all trimesters of pregnancy. If the patient has signs and
265 symptoms of DVT, CUS of the symptomatic leg is undertaken and, if positive, treatment is
266 started. Patients with a negative CUS, and those without symptoms of DVT, have YEARS
267 scoring (see **Table 1**) and a D-dimer test. The D-dimer cutoff for ruling out PE is 1000 ng/ml
268 for those with no YEARS components and 500 ng/ml for those with any YEARS components
269 [61]. This approach has been validated for D-dimer assays with a manufacturer recommended
270 cutoff of 500 ng/ml. The pregnancy-adjusted YEARS protocol reduced radiological imaging
271 by 65% in the first trimester and 32% in the third trimester in a research context [61]. No
272 validation studies have been published, but several are planned [62]. A second prospective
273 study demonstrated the safety of excluding PE in pregnant patients using a standard D-dimer
274 cutoff in combination with the Geneva clinical probability score. [63]. However, a UK
275 observational case-control study recently reported no value to biomarker testing (including D-
276 dimer) [20] and in a secondary analysis of this same cohort, concluded that strategies using
277 clinical probability and D-dimer (YEARS/D-dimer and Geneva/D-dimer) have limited
278 diagnostic accuracy and do not accurately rule out all PE in pregnancy [64]. A health economic
279 analysis by the same group showed that a strategy of scanning all women with a suspected PE
280 appeared optimal. This strategy accrued more Quality Adjusted Life Years (QALYs) and
281 incurred fewer costs than any selective strategy based on a clinical decision rule and was
282 therefore the dominant strategy computed by the model in the pregnant patient [65].

283

284 At present, most guidelines do not support the use of D-dimer testing to exclude PE in
285 pregnancy. Further validation studies of the pregnancy adapted YEARS algorithm may inform
286 future practice. At present, the Royal College of Obstetricians and Gynaecologists in the UK
287 suggest the following approach: routine clinical assessment including bloods, CXR and ECG,
288 then bilateral CUS in the stable patient with leg symptoms, although this is unlikely to be

289 available 24 hours a day in the ED. If all tests are normal and suspicion remains, CTPA or
290 planar V/Q should be considered to enable definitive diagnosis [66]. Shared decision making
291 should take place to consider diagnostic imaging. CT scanning will expose hypertrophied
292 breast tissue to radiation, a risk for later breast cancer. However, V/Q scanning exposes the
293 foetus to a higher dose of radiation. The absolute risk in both scenarios is low [67].

294

295 PE TESTING ALGORITHM OPTIONS

296 Given the diversity of PE testing options, clinicians should employ their preferred approach to
297 testing based chiefly upon their own departmental and national guidance. Choice of diagnostic
298 protocols may depend on available adjuncts, such as availability of a phone app or embedded
299 support within the departmental electronic medical record. Consistency allows for familiarity,
300 proficiency, reliability, and safety within the diagnostic approach. Broadly, there are two
301 approaches to take following initial assessment in a haemodynamically stable patient where
302 PE is suspected:

303

304 Option 1: Wells or Geneva models [Figure 1]

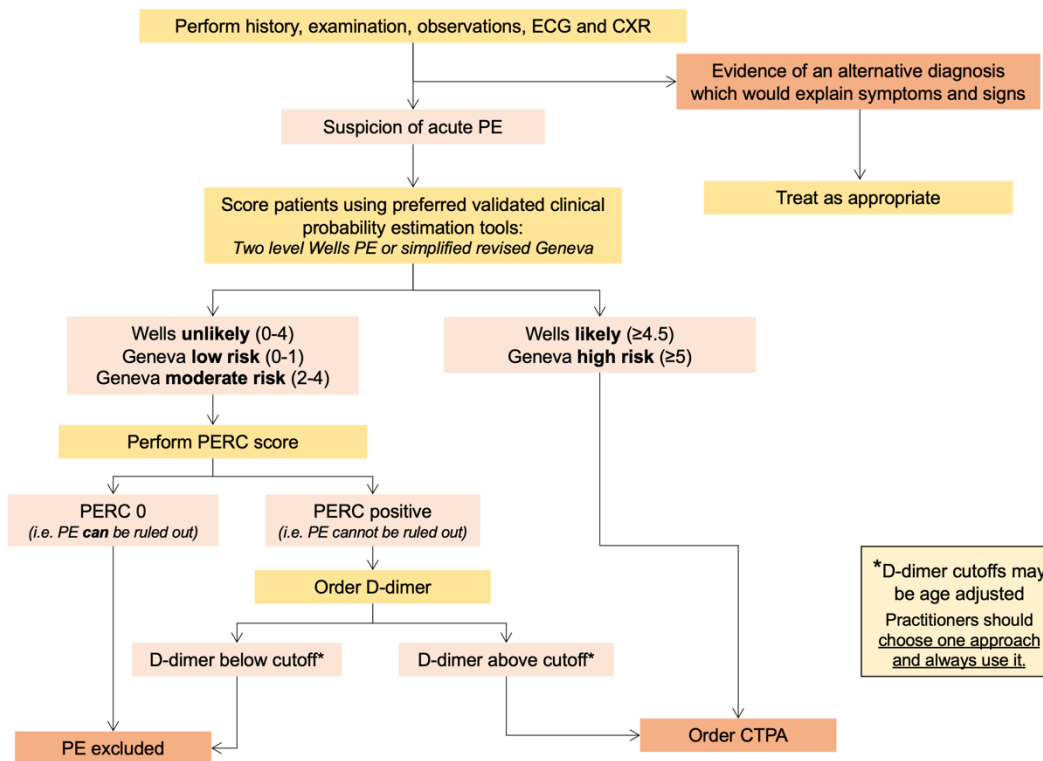
305 Patients should be scored using the Wells or Geneva models. Ensure you document the score
306 in the patient's notes. For Wells unlikely or Geneva low / moderate scoring patients, PERC can
307 be utilised; if PERC is positive then D-dimer testing should be ordered. An age-adjusted D-
308 dimer cut off can be used. If the D-dimer result is above the age-adjusted cut off, diagnostic
309 imaging should be ordered. If D-dimer is below the age-adjusted cut off, PE can be excluded.
310 For patients with a likely Wells score or high probability Geneva score, diagnostic imaging for
311 PE should be arranged without additional testing.

312

313

314 **Figure 1**

315



316

317

318 CTPA: computer tomography pulmonary angiography; CXR: chest X-ray; ECG:
319 electrocardiogram; PE: pulmonary embolism.

320

321 Option 2: YEARS model [Figure 2]

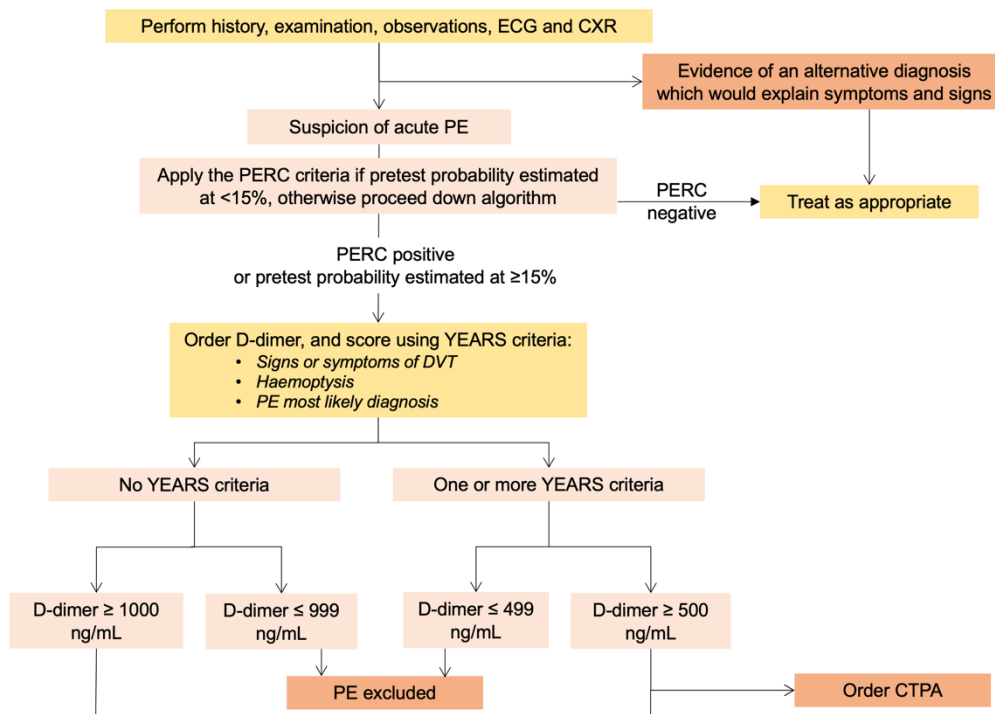
322 D-dimer testing is conducted for all patients with suspected PE who are PERC positive or who
323 have a pretest probability estimated at $\geq 15\%$. Document the presence or absence of the YEARS
324 items (signs or symptoms of DVT; haemoptysis; PE most likely diagnosis) before ordering D-
325 dimer. If no items are present, use a 1000 ng/mL D-dimer cutoff to exclude PE. If one or more
326 items are present, use a 500 ng/mL D-dimer cutoff to exclude PE. Patients with D-dimer results
327 above the YEARS cut off should progress to diagnostic imaging [36]. This approach is
328 supported by the ESC 2019 guidance [25].

329

330

331 **Figure 2**

332



333

334

335 CTPA: computer tomography pulmonary angiography; CXR: chest X-ray; DVT: deep venous
336 thrombosis; ECG: electrocardiogram; PE: pulmonary embolism; PERC: PE rule out criteria.

337

338 SUMMARY

339 Clinical assessment of suspected PE is difficult. The disease presents with a broad spectrum of
340 symptoms, signs and severity and continues to be misdiagnosed, despite being a commonly
341 considered diagnosis in the ED. Whilst clinicians should follow a consistent approach
342 advocated in their local and/or national guidance where possible, they must also weigh up the
343 individualised harms of missed PE against the benefits and harms of investigation / treatment.
344 The importance of timely and confident diagnosis of PE is paramount. However, broad use of
345 diagnostic imaging for PE carries important risks of harm from unnecessary testing. The risks
346 may also vary markedly between patient groups (i.e. PE due to metastatic malignancy versus
347 pregnancy-related PE). Considered and individualised assessment alongside patient
348 engagement and shared decision making are therefore vital aspects of the diagnostic process.

349 Competing interests

350 JC, PS, KdW and MR have no conflicts of interest to declare.

351 DH was a previous topic expert for NICE NG158 and QS201, regarding the diagnosis and
352 management of venous thromboembolic disease and venous thromboembolism in adults,
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