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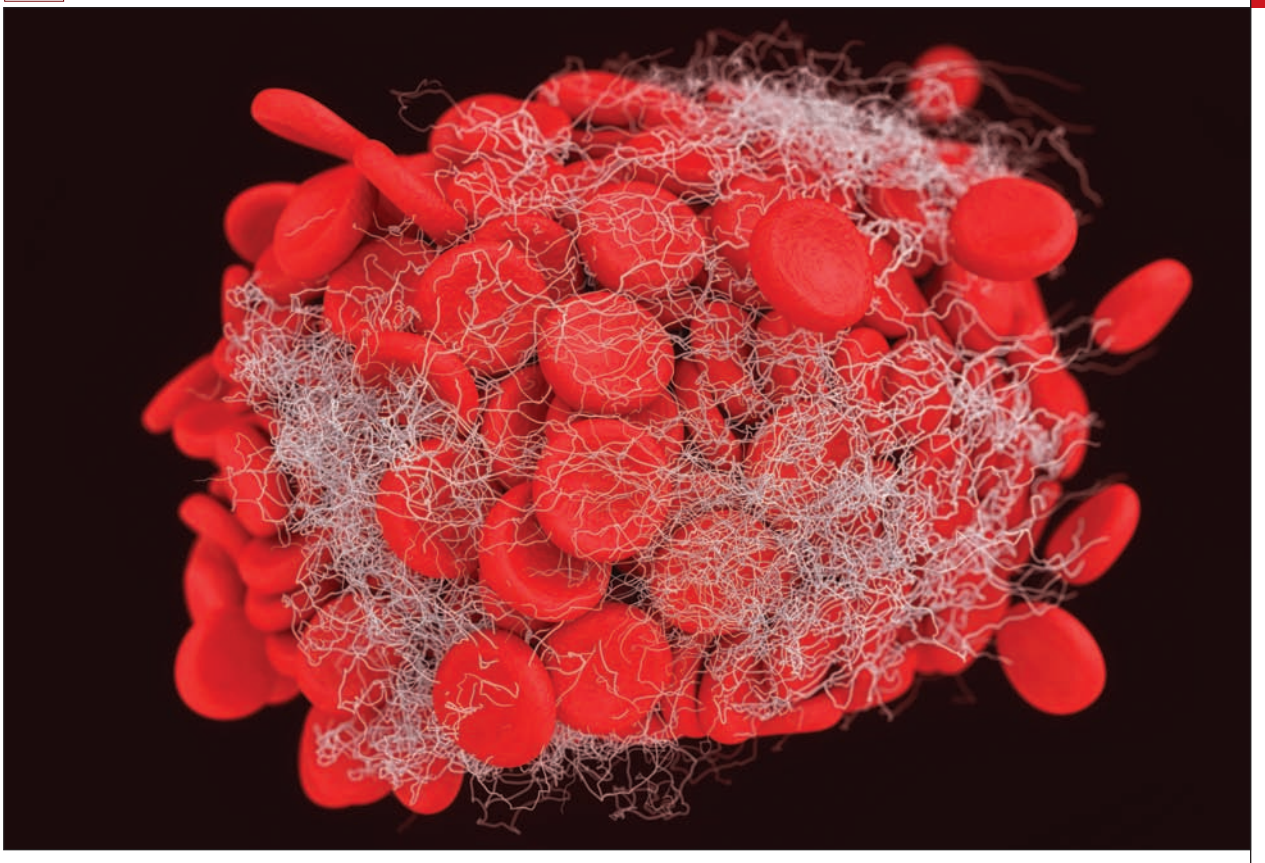

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Diagnosis of venous thromboembolism using clinical pretest probability rules, D-dimer assays, and imaging techniques

Abstract: Venous thromboembolism is a significant clinical entity that includes two associated medical disorders: deep vein thrombosis and pulmonary embolism. The goal of this article is to describe the optimal approach to evaluating venous thromboembolism including pretest probability clinical decision rules and appropriate testing to ensure an accurate diagnosis.

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Venous thromboembolism (VTE) is an important concern in the primary care setting. VTE includes two associated medical conditions: deep vein thrombosis (DVT) and pulmonary embolism (PE). The 1-month case mortality for VTE is between 2.8% and 12%, and a conservative estimate of the economic burden to the US healthcare system is $7 to $10 billion annually for newly diagnosed, medically treated patients.[1,2] Newer evidence-based guidelines suggest the optimal approach to diagnosing VTE includes pretest probability clinical decision rules, D-dimer testing, and appropriate imaging studies.[3,4]

Background

The incidence of VTE is estimated at 0.1% to 0.2% annually with the condition affecting more than

Keywords: clinical pretest probability rule, D-dimer testing, deep vein thrombosis, imaging studies, pulmonary embolism, venous thromboembolism

Risk factors for VTE based on Virchow's triad[5-12]

Virchow's triad		
Venous stasis	**Endothelial injury**	**Hypercoagulopathy**
		Acquired
Immobilization	Prior thrombotic event	Oral contraceptives
Presence of venous central catheter		Pregnancy
Recent major surgery		Hormone replacement therapy
Trauma		
		Malignancy
		Myeloproliferative disease
		Cardiovascular disease
		Chronic kidney disease
		Liver disease
		Inherited
		Excess procoagulant activity, for example, Factor V Leiden and Prothrombin 20210A thrombophilia
		Anticoagulant protein deficiency, for example, antithrombin III and proteins C and S
		Antiphospholipid syndrome, for example, Lupus anticoagulant (prothrombotic antibody)

1 million patients yearly.[3,4] The occurrence increases with age, which is significant since the aging population that is predisposed to risk factors for VTE, such as cancer and cardiovascular disease, is expected to increase.[2] The pathogenesis, elucidated by Virchow's triad, maintains that venous thrombosis occurs due to venous stasis, injury to the endothelium of blood vessels, and either inherited or acquired hypercoagulopathy (see *Risk factors for VTE based on Virchow's triad*).[5-12] Inherited etiologies include clotting factor mutations (Factor V Leiden and prothrombin gene) and deficiencies of natural substances that help inhibit thrombosis such as protein S, protein C, and antithrombin III.[13,14] Acquired risk factors include cancer, cardiovascular disease, and oral estrogen therapy, among others.[6,15] Most DVTs are in the lower extremities (LE), with upper extremity (UE) DVTs accounting for only about 1% to 4% of all events.[16] While the risk factors described above can lead to UE or LE DVTs, some factors specifically associated with UE DVT risk include pacemakers and central venous catheters.[16,17] Congenital or acquired anatomic abnormalities are also possible, although less common, causes of UE DVT.

Prevention of reoccurrence is of vital importance, especially considering that VTE may reoccur as quickly as within months of the initial incident and recurs at the rate of 10% at 1 year and 36% at 10 years.[18]

Additionally, coronavirus disease 2019 (COVID-19) has been correlated with increased risk of VTE, although reported prevalence varies widely due to differing study characteristics.[19] Patients with COVID-19 who require ICU level care may be at especially increased risk.

Postthrombotic syndrome, a complication of DVT, may develop in 20%-50% of patients with DVT due to venous hypertension caused by venous obstruction or valvular reflux due to damaged venous valves.[20] Certain factors increase the risk of development of postthrombotic syndrome, such as location of the DVT (higher risk with proximal than distal location), preexistent venous insufficiency, obesity, increased age, certain treatment-related factors, and presence of residual thrombosis 3-6 months after acute DVT.[20]

This article will focus on evaluation and diagnosis of VTE in a nonpregnant, adult population.

Clinical presentation

The clinical presentation of an acute DVT may include swelling, pain, and erythema of the involved extremity. Dilated veins may be present.[15] A palpable cord may be appreciated and may indicate superficial thrombophlebitis, which often co-occurs with DVT.[21] Patients frequently report pain and tenderness in the calf or medial thigh along the course of major veins, as well as tenderness on dorsiflexion of the foot, known as Homan's sign, with LE DVTs.[21] However, it is important to recognize that Homan's sign is very unreliable. Shoulder, neck, or axilla pain and superior vena cava syndrome are other possible features of UE DVT.[16]

The clinical manifestations of postthrombotic syndrome can include leg pain, swelling, skin discoloration, sensation of heaviness or fatigue of the leg, venous claudication, and venous ulceration.[20] Similarly, arm swelling, pain, heaviness, and dependent cyanosis and

superficial venous dilation of upper arm and chest wall may be signs and symptoms of postthrombotic syndrome following UE DVT.[16,20]

Patients with PE may exhibit signs or symptoms including dyspnea at rest or on exertion, orthopnea, cough, hemoptysis, tachypnea, tachycardia, hypoxia, or pleuritic pain. Symptoms can be mild or nonspecific, and some patients are asymptomatic.[22,23] Crackles or decreased breath sounds may be present on respiratory exam, and the cardiac exam may demonstrate a prominent pulmonic component of the second heart sound.[22,23] Jugular vein distension and fever may also be present. Because PE is frequently a consequence of DVT, calf or thigh pain and swelling may be present.[22]

Diagnosis of VTE

The diagnosis of VTE is best accomplished using an algorithmic approach that utilizes three concepts: clinical pretest probability rules (CPPR), D-dimer testing, and imaging.

CPPR

The most commonly used CPPR for LE DVT is the Wells rule.[4,24] It uses nine objective clinical features that are assigned a score of 1 point each (such as certain risk factors, signs and symptoms, and history of DVT) and a subjective variable (alternate diagnosis at least as likely as DVT), which is assigned a score of -2 (see *Wells clinical decision rule for LE DVT*).[3,4,24] The use of this decision rule allows the clinician to predict the probability of a DVT. A score of -2 to 0 is a low probability, 1 to 2 is moderate probability, and ≥3 indicates a high probability of DVT. The modified decision score involves two probability categories: <2 indicates DVT is unlikely and ≥2 indicates DVT is likely.[3,4,24] This score can easily be tabulated by using a free app, Calculate by QxMD, which is available in both the App Store for Apple devices and on Google Play.[25] The Hamilton rule is another CPPR that can be used to predict likelihood of DVT (see *Hamilton clinical decision rule for DVT*).[26] There are seven items worth 1-2 points each. A score of ≤2 indicates that the probability of DVT is unlikely, while a score of ≥3 indicates that it is likely.[26]

A CPPR for UE DVT is the Constans score (see *Constans clinical decision score for UE DVT*).[17,27,28] Of note, this scoring tool was validated only in an inpatient population.[31] It includes three characteristics worth 1 point each (central venous catheter or

Wells clinical decision rule for LE DVT[3,4,24]

Clinical characteristics	Score
Active cancer	1
Paralysis, paresis, or recent plaster immobilization of the lower extremities	1
Recently bedridden >3 days or major surgery (12 weeks) requiring general or regional anesthesia	1
Localized tenderness along the deep venous system	1
Swelling of entire leg	1
Calf swelling ≥3 cm larger than asymptomatic side	1
Pitting edema confined to the symptomatic leg	1
Collateral superficial veins (nonvaricose)	1
Previously documented DVT	1
Alternative diagnosis at least as likely as DVT	-2

Score interpretation	Probability	*Patient population	Prevalence
≤0	Low	60%	5%
1-2	Moderate	30%	25%
≥3	High	10%	60%
Modified decision score			
<2	Unlikely	54.3%	5.5%
≥2	Likely	45.7%	27.9%

*Percentage of patients within a given score category

Hamilton clinical decision rule for DVT[26]

Clinical characteristics	Score
Immobilization of the lower limb	2
Active malignancy	2
Strong clinical suspicion of DVT without other diagnostic possibilities	2
Male gender	1
Bedrest or recent surgery	1
Calf circumference difference >3 cm	1
Erythema	1

Score interpretation	Probability	*Patient population	Prevalence
≤2	Unlikely	63%	11%
≥3	Likely	37%	38%

*Percentage of patients within a given score category

Constans clinical decision score for UE DVT[17,35]

Patient characteristic	Score
Central venous catheter or pacemaker	1
Localized pain	1
Unilateral edema	1
Other plausible diagnosis	-1

Score interpretation	^Probability	*Patient population	Prevalence
≤0	Low	24%	12%
1	Intermediate	40%	20%
≥2	High	36%	70%

^Low- and intermediate-probability groups (score of ≤1) comprise the category of UE DVT unlikely. High probability is classified as UE DVT likely.
*Percentage of patients within a given score category

pacemaker, localized pain, unilateral edema) and one worth -1 point (other plausible diagnosis). Low and intermediate probability groups (a score of ≤1) are classified as UE DVT unlikely; high probability (a score of ≥2) is classified as UE DVT likely.[17,27,28] Prevalence of UE DVT among the low-risk group is 12% and among the high-risk group, 70%.

CPPRs are also widely used for the diagnosis of PE. The first of these tools was developed in the early 1990s by the Prospective Investigation of Pulmonary Embolism Diagnoses (PIOPED) study that improved the diagnostic workup of patients with suspected PE.[29] This has now been replaced by new CPPRs including the Wells rule for PE.[3,4] The revised Wells score for PE includes six objective variables, such as tachycardia, hemoptysis, VTE risk factors, and symptoms of DVT, and one subjective variable (other diagnosis less likely than PE), each with assigned point values (see *Wells clinical decision rule for PE*).[3,4] Scores indicate low, moderate, or high probability of PE. A score of >4, which combines the moderate- and high-probability groups, indicates a likely PE diagnosis requiring further evaluation. Of note, although this CPPR has been used in studies of the diagnostic strategy recommended for patients with recurrent PE, it hasn't been specifically validated for those patients.[27]

Additionally, a clinical prediction rule, the Pulmonary Embolism Rule-out Criteria (PERC), is quite expedient for PE.[30] This tool was developed for the evaluation of patients that present to the ED with suspected PE. The variables in these rule-out criteria include age <50 years, heart rate <100 beats/minute, pulse oximetry >94% on room air, no unilateral leg swelling, no hemoptysis, no recent surgery or trauma, no prior PE or DVT, and no oral hormone use. PERC doesn't assign low, intermediate, and high probability like the Wells rule; instead it identifies patients who don't require diagnostic testing for PE, namely, patients who have both a low probability of PE and meet all eight of the criteria.[3] Only 2% of patients with all negative clinical factors were found to have a PE. This assessment is easily accomplished and can help avoid unnecessary imaging.

Application of CPPRs

Case 1. A 40-year-old male presents with right leg swelling which began 1 day ago. He is in otherwise good health and takes no medications. His vital signs are stable: temperature 98.6° F (37° F), heart rate 72 beats/minute, respiratory rate 14, BP 120/80. His

oxygen saturation on room air is 99%. Cardiac, pulmonary, and abdominal exams are unremarkable. His right leg has localized tenderness along the right saphenous vein. His right calf measures 42 cm and left calf, 38 cm. There is pitting edema along the entire right leg and no edema in the left leg. The Wells DVT CPPR indicates this patient has a high probability for DVT with a score of 4 points, including one point each for localized tenderness along the deep venous system, swelling of the entire leg, calf swelling ≥ 3 cm larger than the asymptomatic side, and pitting edema only in the symptomatic leg.

Case 2. A 63-year-old female presents to the practice with dyspnea and chest discomfort described as tightness and difficulty catching her breath. The onset was sudden. She has breast cancer and had a left mastectomy 4 weeks prior to presentation. She is currently undergoing chemotherapy. Her vital signs are heart rate 106 beats/minute, respiratory rate 28, and BP 130/85. She is afebrile and her oxygen saturation is 97% on room air. Significant physical exam findings include lungs that are clear to auscultation except for occasional wheezing in the right lung field. Bilateral LE swelling and minimal left calf tenderness is present. Her chest X-ray demonstrates no infiltrates or effusions, and her ECG shows sinus tachycardia, an incomplete right bundle-branch block and an $S_1Q_3T_3$ pattern. Using the Wells PE CPPR, the probability of a PE in this patient is likely with a score of 10 including signs or symptoms of DVT, tachycardia >100 beats/minute, surgery in the previous 4 weeks, and presence of malignancy, with other diagnoses less likely than PE. The ECG with $S_1Q_3T_3$ is also consistent with acute cor pulmonale associated with PE (McGinn-White sign).[31]

Case 3. A 42-year-old female presents with a chief concern of awaking the morning of presentation with right pleuritic intrascapular pain not associated with cough, hemoptysis, fever, or chills. She reports no anterior chest pain, leg pain, edema, or shortness of breath. She has not traveled recently and takes no medications including oral contraceptive agents. Her past medical history is unremarkable and there is no personal or family history of VTE. Her physical exam reveals normal vital signs and oxygen saturation with good breath sounds bilaterally and no edema of extremities. Using PERC, this patient has no history or symptoms related to PE and has a very low probability of VTE.

D-dimer testing

D-dimer is one of the protein fragments produced when thrombolysis occurs in the body. Normally, it is either undetectable or found at very low levels; elevated levels imply that the body is breaking down blood clots.[32-34] D-dimer levels are almost always increased in VTE, and a normal level helps to exclude DVT and PE. D-dimer can be used to eliminate the need for further testing for patients who have a low calculated clinical probability using the appropriate CPPR. However, because D-dimer levels can increase in other conditions, an abnormal result does not confirm VTE. Additionally, false-positive results occur more frequently in older patients.[34]

The sensitivity of the D-dimer is an important consideration when used to help with both the diagnosis and treatment plan for patients with VTE. Adjusted D-dimer assays and levels have been proposed to improve the value of VTE diagnosis. D-dimer assays may be categorized into high or moderate

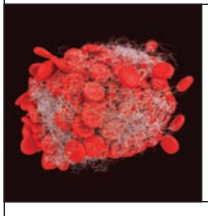
Wells clinical decision rule for PE[2-4]

Clinical characteristic	Score
Clinical symptoms of DVT (leg swelling, pain with palpation)	3
Other diagnosis less likely than PE	3
Tachycardia (>100 bpm)	1.5
Immobilization (≥3 days) or surgery in the previous 4 weeks	1.5
History of DVT or PE	1.5
Presence of hemoptysis	1
Presence of malignancy	1

Score interpretation	^Probability	*Patient population	Prevalence
≤4	Low	60%	5%
4.5-6	Moderate	30%	25%
≥6	High	10%	60%

^The low probability group is categorized as PE unlikely. Moderate- and high-probability groups together comprise the category of PE likely (score of >4).
*Percentage of patients within a given score category

sensitivity, depending on the measurement technique and level of positive or negative D-dimer.[3] A high sensitivity D-dimer assay has a sensitivity of ≥95%, but a specificity of only about 40% in outpatients, and even lower in inpatients.[3] A negative highly sensitive test can be used to rule out VTE in patients with a low probability based on a CPPR but is found in only about 30% of outpatients, so additional diagnostic imaging is often needed. Moderately sensitive tests have a sensitivity of 80% to 94% and a specificity up to 70% in outpatients. To exclude DVT or PE using a moderately sensitive test, an additional assessment or test result is needed along with a negative D-dimer result. In patients with suspected DVT, this includes either a low CPPR score or a negative venous ultrasound. In patients suspected of PE, this includes a low CPPR score or a nondiagnostic ventilation-perfusion (V/Q) scan (or computed tomography pulmonary angiogram [CTPA]) along with negative bilateral proximal venous ultrasound.[3]



Patients deemed low-risk by a CPPR such as the Wells rule who are suspected of LE DVT should be evaluated using a highly sensitive D-dimer assay.

In the past, a single cutoff value for D-dimer has been used to determine a negative assay. Recently, it has been suggested that increasing the specificity of D-dimer testing can be accomplished without compromising a negative predictive result called the "adjusted CPPR" based on the pretest probability values.[3] Specifically, using a D-dimer of <1,000 mcg/L is suggested in patients with a low CPPR score because they have a low prevalence of disease; a D-dimer of <500 mcg/L should be used in patients with a moderate CPPR score. This approach has been validated prospectively in patients with suspected DVT.[3] Additionally, an "age adjusted" approach has been prospectively validated in patients with suspected PE.[3] A D-dimer threshold of <500 mcg/L is recommended to exclude VTE in patients 50 years of age or younger, and in those over 50, a threshold equal to 10 times the patient's age should be used. For example, in a 65-year-old patient, a D-dimer <650 mcg/L excludes VTE. This approach increases the specificity of D-dimer testing without compromising sensitivity.[3] Prospective validation of the age-adjusted D-dimer threshold to rule out DVT is currently ongoing.[35]

Imaging strategies for DVT

The American Society of Hematology (ASH) guidelines provide recommendations for imaging for patients with suspected DVT.[27,28] The guideline uses clinical probability estimation, such as Wells scores indicating low, medium, or high risk, for both LE and UE DVT.

Imaging for LE DVT. Patients deemed low-risk by a CPPR such as the Wells rule who are suspected of LE DVT should be evaluated using a highly sensitive D-dimer assay. If the D-dimer results are negative, no further testing or treatment for DVT is needed. If D-dimer results are positive, a proximal LE or whole-leg ultrasonography should be ordered. Moderate-risk patients should be evaluated first with ultrasound of the leg. A negative ultrasound of the whole leg requires no further evaluation; however, a negative finding on only an initial proximal ultrasound should be followed by a repeat ultrasound in 1 week if no other diagnosis is identified. Patients identified as high-risk by CPPR should have initial ultrasound with confirmation of negative results with repeat ultrasound in 1 week, unless an alternative diagnosis is discovered.[27]

The guidelines are different for the evaluation of a recurrent LE DVT; D-dimer assay is suggested for those with a low probability based on a CPPR, followed by a proximal ultrasound to confirm positive results. All patients with intermediate or high probability should have proximal ultrasonography. Importantly, if prior imaging is available, previous and current images should be compared to determine whether the findings are consistent with recurrent DVT.[27]

Imaging for UE DVT. ASH guidelines for UE DVT use the Constans score.[17,27,28] Patients classified as unlikely (low- or intermediate-probability) should be evaluated with a high-sensitivity D-dimer with no further testing or treatment required for a negative result. A positive D-dimer requires a follow-up duplex ultrasound. This recommendation is based on expert opinion and is considered clinically appropriate but does not have the ability to completely rule out UE DVT. Patients classified as likely, or high-risk, should receive either a high-sensitivity D-dimer

followed by duplex ultrasound, or initial duplex ultrasound that is repeated in 1 week. High-risk patients can only be ruled out for UE DVT by one of these two methods.[35]

Imaging for PE.

ASH guidelines use probability estimates, such as the Wells PE CPPR scores of low, intermediate, and high.[27] PERC may be used for patients with low probability of PE (based on a CPPR), to determine whether D-dimer testing is needed.[27] For patients with low probability who do not meet all the criteria of PERC and for those at intermediate probability, a high-sensitivity D-dimer should be ordered. A negative assay in this group requires no further evaluation or treatment. Patients with a positive D-dimer result should receive either a V/Q scan or a CTPA.[27]

The guidelines recommend a V/Q scan in order to limit radiation exposure.[27] However, the study must be read expeditiously, and increasing age and intrinsic lung disease increase the risk of a nondiagnostic V/Q scan.[35] For these reasons, a CTPA is commonly ordered as the initial imaging test in clinical practice. A proximal LE ultrasound or a CTPA can be considered for a nondiagnostic V/Q scan although the guideline recommends CTPA in this situation.[27,35]

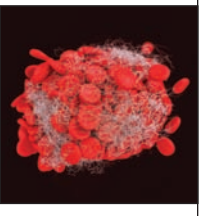
CTPA is recommended for high-risk patients, although a V/Q scan can be used as an initial test if CTPA is unavailable, as long as it's followed by further testing if nondiagnostic.[27] A negative CTPA should be confirmed with a proximal LE ultrasound or V/Q scan, but not D-dimer, before ruling out PE.[27,35]

For suspected recurrent PE, the guidelines recommend a D-dimer assay for patients with low and intermediate pretest probability, followed by CTPA if the D-dimer test is positive. CTPA should be ordered as initial imaging for patients with a high pretest probability. If available, prior imaging should be compared with the new angiogram to determine recurrent or residual PE.

Conclusions

DVT is a common medical concern in the primary care setting. NPs need to be well versed in the recommendations to ensure a timely and accurate diagnosis and prevent the mortality and morbidity associated with these thromboembolic disorders. Probability rules differ among outpatients and hospitalized patients, and the appropriate CPPR should always be part of the initial assessment to help triage patients. The availability of D-dimer testing as well as the sensitivity and specificity of the test being used are important considerations in the preliminary workup of the patient. Imaging with ultrasound for LE DVT in the US almost exclusively involves a whole leg evaluation; in Europe, proximal ultrasound is used because clots below the knee are not routinely treated. PE can be an elusive diagnosis with some patients presenting with only minor symptoms, such as a cough. An algorithmic approach is essential to safely diagnose VTE. This article provides a gestalt for the evaluation of VTE including history, physical exam, probability estimation, and diagnostic testing.

An algorithmic approach is essential to safely diagnose VTE.



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