Venous Thromboembolism and Associated Prothrombotic Disorders in the Intensive Care Unit

- Venous thromboembolism (VTE), which includes deep vein thrombosis (DVT) and pulmonary embolism (PE), is a common cause of morbidity and mortality affecting over 600,000 Americans each year and causing up to 50,000 deaths .

- in a prospective multicenter study of thromboprophylaxis in the intensive care unit (ICU) patients, 7.7% of patients developed VTE despite thromboprophylaxis

RISK FACTORS

- Recognizing the conditions that predispose patients to VTE is essential because more than 60% of PE-related deaths occur in patients who go untreated, because the diagnosis was unsuspected and, therefore, undetected.
- Virtually, all the identified risk factors for VTE can be classified into one of the three classic components of Virchow triad of stasis, venous injury, and hypercoagulability described nearly 150 years ago

TABLE 92.1 Risk Factors for First Episode of Venous Thromboembolism

Genetic Risk Factors
Antithrombin deficiency
Protein C deficiency
Protein S deficiency[a]
Factor V Leiden
Prothrombin gene mutation
Non-O ABO blood group
Dysfibrinogenemia[a]
Elevated factor VIII
Elevated factor IX
Elevated factor XI
Hyperhomocysteinemia (including homocystinuria)[a]

Acquired Risk Factors
Increasing age[a]
Cancer[a]
Antiphospholipid syndrome[a]
Infections (HIV, sepsis, etc.)[a]
Inflammatory disorders (e.g., SLE, IBD, vasculitis, etc.)[a]
Nephrotic syndrome
Obesity
Smoking
Environmental
Surgery (major inpatient, ambulatory)[a]
Trauma[a]
Immobilization
Central venous catheter
Pregnancy/postpartum
Hormonal therapy (e.g., oral, transcutaneous, vaginal ring contraceptive, Depot progestin injections, hormone replacement, etc.)
Chemotherapy
Vena cava filter
Travel

Inherited Hypercoagulable Disorders

Factor V Leiden

Factor V Leiden (FVL) is the most common inherited thrombophilic state affecting 5% of European Americans, 2% of Hispanic Americans, 1% of African Americans and Native Americans, and 0.5% of Asian Americans FVL refers to a point mutation (G1691A), which results in a singl amino acid change (Arg506Gln) at the site in the factor V protein where it is cleaved by activated protein C (PC).

Protein C Deficiency

PC is an important endogenous anticoagulant protein that inactivates activated factors V and VIII. Heterozygous PC deficiency affects 0.2% of the general population and 3.2% of unselected patients with their first episode of VTE .

It is associated with a sevenfold increased risk of VTE . Homozygous PC deficiency is a rare serious thrombophilic syndrome that causes life-threatening thrombotic complications shortly after birth, a condition called ***neonatal purpura fulminans***.

Protein S Deficiency

Protein S (PS) is the nonenzymatic cofactor for activated PC. PS circulates in two forms: approximately 60% is bound to C4b protein whereas the remaining 40% is free. Only free PS has cofactor activity. The incidence of PS deficiency in the general population has been estimated to be 0.03% to 0.13%.

PS deficiency is associated with an eightfold increased risk of VTE , and may be a risk factor for ***arterial thromboembolism***

Antithrombin Deficiency

Antithrombin (AT) inhibits serine protease coagulation factors by binding to the active site of the target serine protease (e.g., thrombin, activated factors X and IX, etc.) and forming an inactive complex. Heterozygous type I AT deficiency is rare, affecting 1 in 2,000 individuals in the population.

It is associated with an 8- to 10-fold increased risk of thrombosis and is present in 1% to 2% of patients with thrombosis . AT deficiency **does not** increase the risk of **arterial** thromboembolism

Dysfibrinogenemia

Dysfibrinogenemia is a rare inherited thrombophilic state caused by mutations in the A*α, Bβ, or γ fibrinogen genes. It affects fewer than 1% of* individuals with VTE.

Acquired dysfibrinogenemia is associated with chronic liver disease and cirrhosis as well as hepatocellular and renal cell carcinoma.

Approximately one-third of cases of dysfibrinogenemia are complicated by thrombosis (venous more commonly than arterial), possibly because of reduced binding to thrombin or inhibition of fibrinolysis.

Hyperhomocysteinemia

Homocysteine is a thiol-containing amino acid that is converted to methionine by methionine synthase with vitamin B12 and 5-methyltetrahydrofolate as cofactors. Homocysteine is also converted to cysteine by cystathionine *β-synthase (CBS) which requires pyridoxine* (vitamin B6) as a cofactor.

Hyperhomocysteinemia has been associated with a 20% increase in cardiovascular disease for each 5 *µmol per L increase in fasting* homocysteine levels

- ***Elevated Coagulation Factor Levels***

Elevated factor VIII (>95 percentile) has been associated with an increased risk of initial and recurrent VTE . Elevated factor VIII levels appear to be inherited, but the responsible genetic alterations have yet to be completely characterized. Inflammatory conditions, which are common among patients in the critical care setting, may also transiently raise factor VIII. Elevated factor IX and XI antigen levels have been associated with a 2.5- and 2.2-fold increased risk of initial VTE, respectively

Acquired Hypercoagulable Disorders

Surgery

In the first 6 weeks after an operation, the risk of VTE is 70-fold that of the general population.

The risk of VTE gradually declines over time to 20-fold that of the general population in postoperative weeks 7 to 12, 9.4- fold at 4 to 6 months postoperation, and 3.7-fold at 10 to 12 months postoperation.

In the Million Women study, hip and knee replacement surgery (7.7 per 1,000 persons-months), cancer surgery (4.4 per 1,000 person-months), hip fracture surgery (3.8 per 1,000 person-months), and vascular surgery (3.1 per 1,000 person-months) were associated with a high risk of VTE

Ethnicity and Medical Illness

Ethnicity is an important risk factor for VTE, with Caucasians and African Americans having a higher incidence of VTE than Hispanics and Asians . Immobility is associated with a 9-fold increased risk of VTE . Increased risk is also associated with infectious illnesses such as HIV and autoimmune disorders such as inflammatory bowel disease and systemic lupus erythematosus (SLE)

Central Venous Catheters

Indwelling central venous catheters (CVCs), particularly common in critically ill patients, increase the propensity for venous thrombosis through a variety of mechanisms, including endothelial damage, blood flow impedance, and serving as a nidus for clot formation.

Symptomatic CVC-associated deep venous thrombosis occurs in 2% to 6% of patients . The risk is even higher with peripherally inserted central catheters (PICCs) which are associated with thrombosis in 14% of critical care patients .

Risk factors for CVC-associated DVT include femoral and subclavian insertion sites, number of catheter lumens and catheter size, PICC versus other CVC, location of catheter tip, history of previous VTE, and presence of active cancer.

Cancer

Cancer is associated with a fourfold to sevenfold increased risk of VTE that varies with the type and extent of cancer and the use of chemotherapy, radiation therapy and growth factors, such as erythropoietic stimulatory agents.

Neoplasms of the pancreas, brain, and stomach place patients at high risk for development of thromboembolism, whereas lung and colon cancers are associated with intermediate risk and breast and prostate cancer are associated with a lower risk.

Compared to squamous cell carcinoma, adenocarcinoma is associated with a higher risk of thromboembolism. Metastatic disease is associated with a higher risk of thromboembolism than localized cancer.

Myeloproliferative Neoplasms

Myeloproliferative neoplasms, in particular polycythemia vera (PV), are associated with an increased risk of arterial thromboembolism and VTE that is mediated, at least in part, by erythrocytosis and the associated increased whole blood viscosity, as well as functional abnormalities in leukocytes and platelets.

Risk factors for thromboembolism include age older than 60 years, a previous history of thromboembolism, poorly controlled erythrocytosis, leukocytosis, thrombocytosis, the presence of additional thrombophilic conditions, the JAK2-V617F mutation, and the presence of cardiovascular risk factors, including diabetes, hypertension,hyperlipidemia, and smoking.

Paroxysmal Nocturnal Hemogobinuria

PNH is a rare clonal hematopoietic stem cell disorder associated with decreased expression of complement regulatory proteins (CD55 and CD59) on blood cell membranes.

This acquired genetic alteration results in chronic intravascular hemolysis, pancytopenia, and a strong predisposition to venous (more common) and arterial (less common) thromboses .

Unusual locations for thrombosis (e.g., mesenteric vein thrombosis) are not uncommon in PNH patients.

Pregnancy and Postpartum

VTE is a leading cause of death in pregnant women. The age-adjusted risk of VTE is at least fivefold higher compared with nonpregnant women.

Pregnancy is accompanied by hormonal changes that increase the prothrombotic potential of the blood that include increases in factor VIII, fibrinogen, von Willebrand factor, and plasminogen activator inhibitor 1 and decreases in free PS.

In addition, decreased mobility, increased venous distensibility, and compression of the inferior vena cava (IVC) and iliac veins by the uterus lead to venous stasis The antepartum risk of VTE is highest in the third trimester.

The immediate postpartum period is associated with the highest risk which declines to baseline by 12 weeks postpartum.

Heparin-Induced Thrombocytopenia

Thrombocytopenia affects approximately 20% of patients in the ICU .

Although heparin-induced thrombocytopenia (HIT) is uncommon in the ICU , prompt recognition and treatment are essential because of the adverse consequences associated with this condition.

Surgical patients (particularly, orthopedic and cardiothoracic) are at high risk for HIT, whereas medical patients are at intermediate risk and obstetric and pediatric patients are at low risk

Major Trauma

Major trauma is an important cause of VTE in the ICU.

Fifty-eight percent of trauma patients develop venographic VTE in the absence of thromboprophylaxis .

Trauma is a potent stimulus for clot formation because it impacts all three elements of Virchow' triad. Patients are immobilized (stasis) for a prolonged period of time and have extensive vascular and tissue damage (vascular wall injury), leading to tissue factor and collagen exposure resulting in activated coagulation (hypercoagulability)

Drug-Induced Hypercoagulable Conditions

Hormonal therapies, including combined estrogen–progestin oral contraceptives and estrogen replacement therapy, are associated with a threefold to fourfold and twofold increased risk of VTE, respectively .

The estrogen vaginal ring and oral, as well as depot medroxyprogesterone, also appears to be associated with increased risk.

The low-dose progestin intrauterine device thus far has not been associated with increased risk .

Selective estrogen receptor modulators tamoxifen and raloxifene; immunomodulatory imide drugs, including thalidomide, lenalidomide, and pomalidomide; erythropoietic stimulatory agents; and atypical antipsychotics, including clozapine, quetiapine, olanzapine, and risperidone; have been associated with an increased risk of thromboembolism

Antiphospholipid Antibody Syndrome

The antiphospholipid antibody syndrome (APS) is an acquired, autoimmune thrombophilic disorder that is associated with an increased risk of venous and/or arterial thromboembolism, recurrent pregnancy losses, thrombocytopenia, renal insufficiency, vasculitis, and cardiac valvular abnormalities.

APS may be primary (not as a result of any immediately apparent underlying autoimmune disorder) or secondary, most commonly in association with rheumatologic diseases such as SLE.

Catastrophic Antiphospholipid Syndrome

Catastrophic antiphospholipid syndrome (CAPS) is a rare (<1% of APSpatients) and potentially life-threatening manifestation of APS characterized by multiorgan (kidneys, brain, skin, liver, etc.) dysfunction as a result of diffuse microvascular thrombosis.

CAPS is often triggered by infections, major surgery, or discontinuation of immunosuppression or anticoagulation.

Almost all patients with CAPS require an ICU level of care.

TABLE 92.2 Clinical Manifestations of Catastrophic Antiphospholipid Syndrome

Organ system	Manifestations
Blood	Coombs positive hemolytic anemia, autoimmune thrombocytopenia, DIC, bone marrow infarct
Brain	Infarcts, encephalopathy, seizure, transient ischemic attack
Heart	Valvular lesions (Libman–Sacks myocardial infarction, heart failure
Kidney	A 50% increase in serum creatinine, severe systemic hypertension (>180/100 mm Hg), and/or proteinuria (>500 mg/24 h)

Lung	Acute respiratory distress syndrome (most common) [68], pulmonary hypertension with normal cardiac output and pulmonary capillary wedge pressure, pulmonary hemorrhage
Skin	Livedo reticularis, skin ulcers, digital ischemia, purpura, skin necrosis
Vasculature	Venous and/or arterial thromboembolism, including deep venous thrombosis, pulmonary embolism, extremity artery thromboembolism, portal vein and inferior vena cava thrombosis, retinal artery and vein thrombosis

DIC, disseminated intravascular coagulation.

PATHOPHYSIOLOGY

The precise sequence of events that leads to venous thrombosis is not fully understood and likely varies based on dynamic interactions between genetic and acquired risk factors.

In one proposed scheme, blood stasis– induced hypoxia or direct vein wall injury results in endothelial disruption or activation with the exposure of tissue factor on the luminal surface of the vessel triggering initiation of the coagulation cascade, leading to thrombin generation and fibrin deposition.

Proximal lower extremity DVT is the most frequent source of PE. In untreated patients with proximal DVT, approximately half will go on to develop PE. Other sources of PE include pelvic, renal, or upper extremity veins, as well as the right heart. Embolism to the lungs typically occurs 3 to 7 days after the development of a DVT.

After traveling to the lungs, a large thrombus may occlude a major pulmonary artery and cause significant cardiovascular symptoms, or it may break up into smaller clots traveling distally, where it is more likely to produce pleuritic chest pain.

Thrombi are most frequently carried to the lower lobes because of preferential blood flow to this location

PREVENTION

Meta-analyses have demonstrated that pharmacologic VTE prophylaxis reduces the risk of symptomatic DVT, PE, and fatal PE by approximately

50% at the expense of a modest increase in major bleeding . UFH, LMWH, and fondaparinux have all been demonstrated to be effective in

medically ill patients .

Three times-daily UFH may be associated with a greater risk of bleeding than twice-daily UFH . In critically ill patients, dalteparin was associated with a lower risk of DVT than twicedaily UFH .

Large prospective multicenter surveys have demonstrated that VTE prophylaxis is underprescribed [98]. Strategies that have been demonstrated to improve prescription of VTE prophylaxis and reduce VTE include computer alerts and mandatory clinical decision support smart order sets

TABLE 92.4 Padua VTE Risk Assessment Model

Clinical characteristic	Score
Active cancer (patient with local or distant metastases and/or in whom chemotherapy or radiotherapy has been performed within 6 mo)	3
Previous VTE (with the exclusion of superficial vein thrombosis)	3
Reduced mobility (bedrest with bathroom privileges for 3 d or more)	3
Known thrombophilia	3
Recent (within 1 mo) surgery or trauma	2
Age ≥70 y	1
Heart and/or respiratory failure	1

Acute myocardial infarction or ischemic stroke	1
Acute infection and/or rheumatologic disorder	1
Obesity (BMI ≥ 30)	1
Ongoing hormonal therapy	1

Low risk 3 points or less; high risk ≥4 points.

BMI, body mass index; VTE, venous thromboembolism.

Adapted from Barbar S, Noventa F, Rossetto V, et al: A risk assessment model for the identification of hospitalized medical patients at risk for venous thromboembolism: The padua prediction score. J Thromb Haemost 8:2450–2457, 2010.

DIAGNOSIS

Recognizing the presence of VTE can be challenging because the signs and symptoms are neither sensitive nor specific for the diagnosis.

Consequently, the most important step in diagnosis is maintaining adequate clinical suspicion .

This goal is best achieved by careful attention to each patient's constellation of risk factors, symptoms, and signs.

Clinical pretest probability models such as the Wells criteria and pulmonary embolism rule-out criteria (PERC) serve as the foundation for diagnostic algorithms for DVT and PE

TABLE 92.5 IMPROVE VTE Risk Assessment Score

Clinical characteristic	Score
Previous VTE	3
Known thrombophilia	2
Lower limb paralysis	2
Active cancer	2
Immobility ≥7 d (including days prior to and during hospital admission)	1
ICU/CCU stay	1
Age >60 y	1

Low risk = 0 to 1 points; moderate risk 2 to 3 points, and high risk 4 or more points.

CCU, coronary care unit; ICU, intensive care unit; VTE, venous thromboembolism.

Adapted from Mahan CE, Liu Y, Turpie AG, et al: External validation of a risk assessment model for venous thromboembolism in the hospitalised acutely-ill medical patient (VTE-VALOURR). Thromb Haemost 112:692–699, 2014.

TABLE 92.6 Caprini VTE Risk Assessment Model

Clinical characteristic	Score
Stroke (<1 mo)	5
Elective major lower extremity arthroplasty	5
Hip, pelvis, or leg fracture (<1 mo)	5
Acute spinal cord injury (paralysis) (<1 mo)	5
Multiple trauma (<1 mo)	5
Age 75 y or older	3
History of DVT/PE	3
Positive factor V Leiden	3
Positive prothrombin gene G20210A mutation	3
Elevated serum homocysteine	3
Positive lupus anticoagulant	3
Elevated anticardiolipin antibodies	3
HIT (do not use heparin or low molecular weight heparin)	3
Other congenital or acquired thrombophilia	3

Family history of thrombosis	3
Age 61–74 y	2
Arthroscopic surgery	2
Malignancy (present or previous)	2
Laparoscopic surgery (>45 min)	2
Patient confined to bed (>72 h)	2
Immobilizing plaster cast (<1 mo)	2
Central venous access	2
Major surgery (>45 min)	2
Age 41–60 y	1
Swollen legs (current)	1
Varicose veins	1
Overweight/obesity (BMI >25)	1
Minor surgery planned	1
Sepsis (<1 mo)	1
Acute myocardial infarction	1
Congestive heart failure (<1 mo)	1
Medical patient at bedrest	1
History of inflammatory bowel disease	1

History of prior major surgery (<1 mo)	1
Chronic obstructive pulmonary disease	1
Serious lung disease including pneumonia (<1 mo)	1
Oral contraceptive or hormone replacement therapy	1
Pregnancy or postpartum (<1 mo)	1
History of unexplained fetal death or recurrent spontaneous abortion (≥3), premature birth with toxemia or growth-restricted infant	1

Low risk 0–1 point early ambulation; moderate risk 2 points heparin 5 000 units sc q12h or pneumatic compression device; high risk 3 to 4 points heparin 5,000 units sc q8h or enoxaparin 40 mg q24h (weight <150 kg) (30 mg sc q24h with creatinine clearance <30 mL/min and weight <150 kg) or enoxaparin 30 mg sc q12h (weight >150 kg) with option to add pneumatic compression device; very high risk 5 or more points high-risk pharmacologic options PLUS pneumatic compression device.

BMI, body mass index; DVT, deep vein thrombosis; HIT, heparin-induced thrombocytopenia PE, pulmonary embolism; VTE, venous thromboembolism.

TABLE 92.7 VTE Prophylaxis Options

Unfractionated heparin: 5,000 units sc q8–12h
7,500 units sc q8 h (obesity dosing BMI ≥40)

Low Molecular Weight Heparin

Dalteparin 5,000 units sc q24h
7,500 units q24h (obesity dosing BMI ≥40) (limited data)

Enoxaparin 40 mg sc q24h (general medical and surgical prophylaxis)
Enoxaparin 30 mg sc q24h (renal dosing; creatinine clearance 20–30 mL/min)
Enoxaparin 40 mg sc q12h (obesity dosing BMI ≥40)
Enoxaparin 30 mg sc q12h (orthopedic surgery prophylaxis)

Pentasaccharide

Fondaparinux 2.5 mg sc q24h
Renal dosing: avoid in patients with CrCl <30 mL/min; caution in patients with CrCl 30–50 mL/min

Direct Thrombin Inhibitors

Dabigatran (oral direct thrombin inhibitor)

110 mg orally 1–4 h after hip replacement surgery when hemostasis has been secured, then 220 mg orally once daily for 28–35 d

(Avoid in patients with CrCl <30 mL/min or epidural/neuraxial analgesia)

Direct Factor Xa Inhibitors

Apixaban (oral direct factor Xa inhibitor)

2.5 mg orally BID ×35 d starting 12–24 h after hip replacement surgery once hemostasis is secured

2.5 mg orally BID ×12 d starting 12–24 h after knee replacement surgery once hemostasis is secured.

Would avoid in patients with CrCl <25

	mL/min or in presence of neuraxial analgesia)
Rivaroxaban (oral direct factor Xa inhibitor)	
10 mg orally once daily ×35 d starting 6–10 h after hip replacement surgery once hemostasis is achieved	
10 mg orally once daily ×12 d starting 6–10 h after knee replacement surgery once hemostasis is achieved	
Avoid in patients with CrCl <30 mL/min and those with neuraxial analgesia	

BID, twice a day; BMI, body mass index; CrCl, creatinine clearance; q, every; sc, subcutaneously; VTE, venous thromboembolism.

Symptoms and Signs

Although most DVT begin in the calf, the presenting symptoms and signs are often not noted until more proximal veins are involved .

The initial clinical manifestations of DVT may include warmth, erythema, swelling, and pain or tenderness and may be acute, progressive, or resolve spontaneously.

Cellulitis, trauma, Baker cyst, or musculoskeletal pain can all cause signs and symptoms similar to acute DVT.

Most patients with acute PE present with at least one of the following: dyspnea, pleuritic chest pain, or tachypnea.

TABLE 92.9 Wells Clinical Pulmonary Embolism Model

Clinical characteristic	Score
Active cancer (patient receiving treatment for cancer within 6 m or currently receiving palliative treatment)	1
Surgery or bedridden for 3 d or more during the past 4 wk	1.5
History of deep venous thrombosis or pulmonary embolism	1.5
Hemoptysis	1
Heart rate >100 beats/min	1.5
Pulmonary embolism judged to be the most likely diagnosis	3
Clinical signs and symptoms compatible with deep venous thrombosis	3

A score of <2 indicates a low probability of pulmonary embolism. A score of 2 to 6 indicates an intermediate probability of PE. A score of more than 6 indicates a high probability of pulmonary embolism.

Kearon C, Ginsberg JS, Douketis J, et al: An evaluation of D-dimer in the diagnosis of pulmonary embolism: a randomized trial. Ann Intern Med 144(11):812–821, 2006.

TABLE 92.10 Revised Geneva Score

Pulmonary Embolism Model (Simplified Version)

Clinical characteristic	Score
Previous PE or DVT	1
Heart rate	
75–94 beats/min	1
≥95 beats/min	2
Surgery or fracture within last month	1
Hemoptysis	1
Active cancer	1
Unilateral lower limb pain	1
Pain on lower limb deep venous palpation and unilateral edema	1
Age >65y	1

A score of <2 indicates a low probability of pulmonary embolism. A score of 2 to 4 indicates an intermediate probability of PE. A score of 5 or more indicates a high probability of pulmonary embolism.

DVT, deep vein thrombosis; PE, pulmonary embolism.

Klok FA, Mos IC, Nijkeuter M, et al: Simplification of the revised Geneva score for assessing clinical probability of pulmonary embolism. Arch Intern Med 168(19):2131–2136, 2008.

TABLE 92.11 Pulmonary Embolism Rule-Out Criteria

Clinical characteristic	Meets criterion	Does not meet criterion
Age <50 y	0	1
Initial heart rate <100 beats/min	0	1
Initial oxygen saturation >94% on room air	0	1
No unilateral leg swelling	0	1
No hemoptysis	0	1
No surgery or trauma within 4 wk	0	1
No history of venous thromboembolism	0	1
No estrogen use	0	1

Pretest probability with a score of 0 is less than 1%.

Derived from Kline JA, Courtney DM, Kabrhel C, et al: Prospective multicenter evaluation of the pulmonary embolism rule-out criteria. J Thromb Haemost 6(5):772–780, 2008.

Diagnosis of Acute Deep Venous Thrombosis

Compression venous ultrasonography is the preferred noninvasive test for the diagnosis of symptomatic proximal DVT, where it has a weighted sensitivity and specificity of 95% and 98%, respectively .

Although it is generally appropriate to initiate or withhold treatment based on the result of the examination, an exception would be when the result is discordant with the clinical assessment.

For instance, a negative compression ultrasound in the context of a high clinical suspicion for DVT would warrant further investigation, such as venography, magnetic resonance imaging (MRI), or computed tomographic venography (CTV).

Duplex ultrasonography is also useful for detecting upper extremity DVT. Limitations of venous ultrasonography include insensitivity for asymptomatic DVT and pelvic vein clots, dependence on operator skill, and difficulty distinguishing acute from chronic DVT in symptomatic patients.

Diagnosis of Acute Pulmonary Embolism

Contrast-enhanced chest CTA is the imaging procedure of choice for PE because it has the capacity to reveal emboli in the main, lobar, segmental, and subsegmental pulmonary arteries, as well as other diseases of the thorax that can mimic PE.

In patients with an intermediate or high probability of PE, an abnormal CTA has a positive predictive value of 92% and 96%, respectively. In patients with a low clinical likelihood of PE, normal findings on CTA had a 96% negative predictive value supporting the use of multidetector CTA as stand-alone imaging for suspected PE in the majority of patients.

This modality can be used in combination with D-dimer to screen low- to intermediate-risk patients with excellent negative predictive value

An Integrated Approach to Venous Thromboembolism Diagnosis

To minimize patient exposure to ionizing radiation and overall health care costs, an efficient and cost-effective approach to VTE diagnosis integrates pretest probability models such as the Wells criteria and PERC, D-dimer testing, and imaging.

In conjunction with D-dimer testing, the Wells criteria have been demonstrated to safely exclude VTE in outpatients with suspected thromboembolism.

The PERC facilitate identification of low-risk patients in whom PE can be ruled out without imaging.

A schematic depiction of the use of the Wells criteria and the Geneva Score in conjunction with the PERC and D-dimer testing in the diagnosis of DVT and PE is displayed in Figures 92.1 and 92.2.

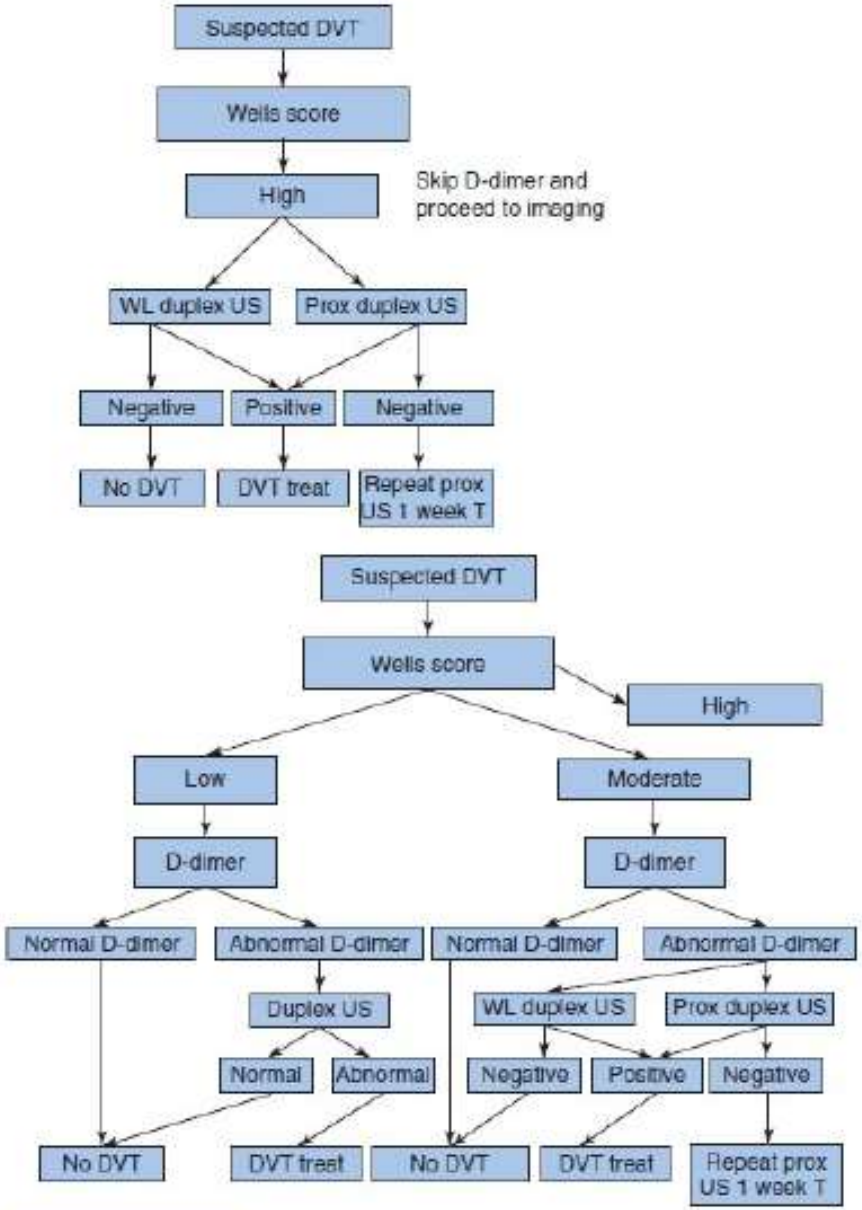

FIGURE 92.1 Diagnostic algorithm for DVT. DVT, deep vein thrombosis.

PERC= Pulmonary embolism rule-out criteria

FIGURE 92.2 Diagnostic algorithm for PE. PE, pulmonary embolism.

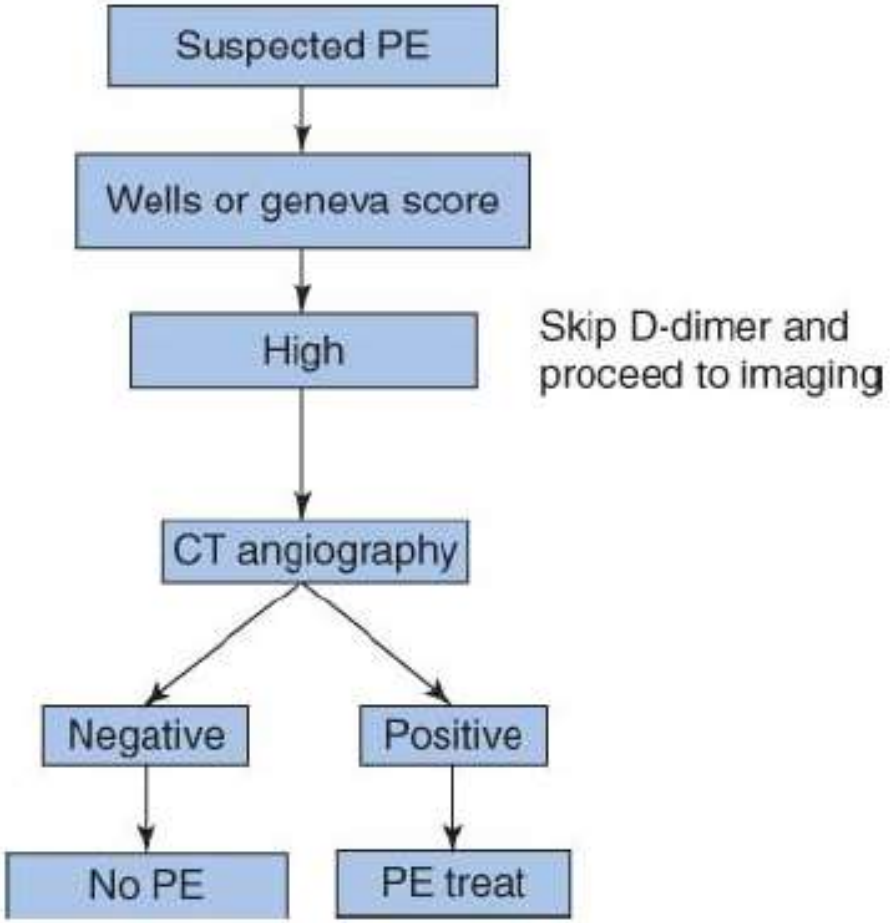

FIGURE 92.3 Anatomic points for venous compression study of the leg.

- ***TREATMENT***

Treatment for VTE centers on the use of anticoagulation to prevent clot propagation and promote the body's natural thrombolytic processes to resorb the clot and allow for vessel recanalization .

Other treatment options include thrombolytic therapy, IVC filter placement, and surgical embolectomy.

Each approach has specific indications as well as advantages and disadvantages. Initiation of therapy should usually be delayed for confirmatory testing in most clinical scenarios.

TABLE 92.15 Treatment Options for VTE

Unfractionated heparin: 80 unit/kg IV bolus followed by 18 units/kg/h infusion adjusted to aPTT ratio

Low Molecular Weight Heparin (LMWH)

Dalteparin 100 units/kg sc q12h or 200 units/kg sc q24h

Renal dosing: no official recommendation-use with caution, consider LMWH anti-Xa levels monitoring and dose adjustment

Enoxaparin 1 mg/kg sc q12h or 1.5 mg/kg sc q24h

FDA approved renal dosing- 1mg/kg sc q24h (CrCl <30 mL/min)

Tinzaparin 175 units/kg sc q24h

Renal dose: same (no evidence of bioaccumulation in the IRIS study)

Pentasaccharide

Fondaparinux 5–10 mg sc q24h (5 mg for weight <50 kg, 7.5 mg for weight 50–100 kg, and 10 mg for weight >100 kg)

Renal dosing: avoid in patients with CrCl <30 mL/min; caution in patients with CrCl 30–50 mL/min

Direct Thrombin Inhibitors

Argatroban[a]

2 g/kg/min continuous IV infusion adjusted to an aPTT ratio of 1.5–3.0 (check first aPTT after 2 h initiation and after each dose change (normal hepatic function)

0.5 µg/kg/min continuous IV infusion (Child–Pugh Classes B and C patients)

Bivalirudin[b]

CrCl >60 mL/min 0.15 mg/kg/h IV infusion

CrCl 45–60 mL/min 0.075 mg/kg/h IV

CrCl 30–44 mL/min 0.05 mg/kg/h IV

CrCl <30 mL/min or renal replacement therapy 0.025 mg/kg/h IV

Dabigatran (oral direct thrombin inhibitor)

150 mg orally BID after 5–10 d of initial parenteral anticoagulation

(Avoid in patients with CrCl <30 mL/min and liver impairment with transaminase >2× ULN))

Direct Factor Xa Inhibitors

Apixaban (oral direct factor Xa inhibitor)

10 mg orally BID ×7 d then 5 mg orally BID

In patients with at least two of the following characteristics: age ≥80 y, body weight ≤60 kg, or serum creatinine ≥1.5 mg/dL, the recommended dose is 2.5 mg orally BID.

Would avoid in patients with CrCl <25 mL/min or sCr >2.5 mg/dL or hepatic dysfunction (AST/ALT >2X ULN or bilirubin >1.5× ULN)

Edoxaban (oral direct factor Xa inhibitor)

60 mg orally once daily

30 mg once daily if CrCl 15–50 mL/min or body weight ≤60 kg or avoid in patients with CrCl <15 mL/min or Child–Pugh class B/C hepatic impairment

Rivaroxaban (oral direct factor Xa inhibitor)

15 mg orally BID ×3 wk followed by 20 mg once daily

Avoid in patients with CrCl <30 mL/min and Child–Pugh class B/C

Vena cava filter

[a]Argatroban dosing per package insert at: https://www.gsksource.com/pharma/content/dam/GlaxoSmithKline/US/en/Prescribing_Information/Argatroban/pdf/ARGATROBAN.PDF. Accessed December 29, 2015.

[b]Adapted from Kiser TH, Mann AM, Trujillo TC, et al: Evaluation of empiric versus nomogram-based direct thrombin inhibitor management in patients with suspected heparin-induced thrombocytopenia. Am J Hematol 86:267–272, 2011.

ALT, alanine transaminase; aPTT, activated partial thromboplastin time; AST, aspartate transaminase; BID, twice a day; CrCl, creatinine clearance; FDA, Food and Drug Administration; IV, intravenous; sc, subcutaneously; q, every; ULN, upper limit of normal; VTE, venous thromboembolism.

- ***Anticoagulation***

Anticoagulants do not directly dissolve preexisting clot; instead, they prevent thrombus extension and indirectly decrease clot burden through the body's endogenous fibrinolytic system. Information regarding pharmacokinetics and dosing of traditional anticoagulants such as UFH, the LMWH, fondaparinux, and warfarin .

For critically ill ICU patients, UFH is the parenteral anticoagulant of choice given its short half-life and complete reversibility with protamine. Multiple clinical trials have demonstrated that LMWH is a safe and effective alternative to UFH for the treatment of acute VTE that does not require laboratory monitoring [150]. Similarly, fondaparinux, a synthetic pentasaccharide, is as effective as LMWH and UFH in the initial treatment and prevention of VTE . Although fondaparinux is an attractive agent for outpatient anticoagulation because of its extremely rare association with HIT, it is often an impractical anticoagulant in ICU patients owing to its long half-life, renal elimination, and the absence of an available reversal agent.

- ***Thrombolytic Therapy***

In patients with PE, systemic thrombolytic therapy is reserved for patients with massive PE characterized by the presence of hypotension (systolic blood pressure <90 mm Hg) and hypoxemia (room air O2 saturation <90%) in whom mortality rates can be as high as 58% .

Thrombolytic therapy is not generally used in patients with submassive PE.

In two randomized controlled trials in patients with submassive PE, thrombolytic therapy prevented clinical deterioration but was not associated with a mortality benefit and increased bleeding complications so it should be reserved for patients with massive PE

Catheter-directed thrombolysis (CDT) using the EKOS ultrasound catheter may be a useful option for patients with massive or submassive PE deemed at high risk for bleeding who are also at high risk for clinical deterioration as a result of their PE.

The EKOS catheter uses ultrasound to disrupt the structure of the thrombus while spraying the thrombolytic agent locally into the substance of the clot via side holes in the catheter.

TABLE 92.16 Thrombolytic Treatment Regimens for PE

Streptokinase 250,000 units IV (loading dose during 30 min); then 100,000 units/h for 24 h
Urokinase[a] 2,000 units/lb (or 4,400 units/kg) IV (loading dose during 10 min); then 2,000 units/lb/h (or 4,400 units/kg/h) for 12–24 h
Alteplase tPA 100 mg IV during 2 h

[a]Limited availability.

IV, intravenous; PE, pulmonary embolism; tPA, tissue plasminogen activator.

TABLE 92.17 Contraindications to Thrombolysis

Absolute
History of hemorrhagic stroke or stroke of unknown origin
Intracranial tumor
Ischemic stroke in previous 3 mo
History of major surgery, trauma, head injury within previous 3 wk
Platelet count below 100,000/μL
Active bleeding
Bleeding diathesis
Relative
Age >75 y
Pregnancy or first postpartum week
Noncompressible puncture sites
Traumatic resuscitation
Refractory hypertension (systolic blood pressure >180 mm Hg; diastolic blood pressure >100 mm Hg)
Advanced liver disease
Infective endocarditis
Recent gastrointestinal bleed (within 3 mo)
Life expectancy ≤1 y