Workup and Treatment of Pulmonary Embolus

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Introduction

Neurosurgical patients present a special challenge in the diagnosis and treatment of venous thromboembolism (VTE) and pulmonary embolism (PE). First, neurosurgical patients are generally at high risk of VTE/PE due to factors related to malignancy, immobilization, or the postoperative state. Second, medical VTE prophylaxis and treatment with systemic anticoagulation are sometimes contraindicated in neurosurgical patients. In general, there is little data to inform decision-making in specific difficult patient scenarios.

Definitions and Classifications

VTE consists of deep venous thrombosis (DVT) and PE. DVT typically occurs in the veins of the pelvis, lower extremities, or upper extremities, and a PE is a thrombus which originates elsewhere in the body, such as within the deep veins of the pelvis or lower extremity, and lodges in the pulmonary artery and/or its branches. Specifically, the iliac, femoral, or popliteal veins are the most common sites of PE origin, although in certain patient populations, such as those with malignancy, a PE source in the extremities or pelvis may not necessarily be demonstrated [1]. With respect to DVTs in the calf veins, approximately a third will progress proximally resulting in a concomitant increase in the likelihood of embolization [2, 3].

Pulmonary emboli may be classified as acute, subacute, or chronic depending on the timing and type of symptoms. In acute PE, symptoms referable to pulmonary artery obstruction develop immediately, while in chronic PE, patients may develop pulmonary hypertension over time. Acutely, a PE may result in impairment of gas exchange, pulmonary infarcts, right heart dysfunction, and hypotension (SBP <90 mmHg). The occurrence of hypotension is an important clinical sign because it has important prognostic and therapeutic consequences, i.e., it portends a poor prognosis and may require emergent thrombolysis or mechanical embolectomy. The severity of the clinical presentation is also sometimes used to classify patients into those with massive, submassive, or nonmassive PE [4].

Additional classifications refer to the location of the PE within the pulmonary artery and branches. This is of importance specifically

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because proximal localization (i.e., within the pulmonary artery trunk or at the bifurcation, the so-called saddle PE) is more likely to result in hemodynamic dysfunction and poor outcome.

Epidemiology of VTE

In the United States, the incidence of DVT has been reported as 422/100,000 [5]. The incidence of PE averages approximately 100/100,000 depending on the data source, and some sources have reported that up to 40 % of patients diagnosed with DVT experience PE [6]. Mortality in acute PE in the United States varies from 1 to 10 % of patients diagnosed with PE depending on the study and whether all-cause mortality was included [7]. Among patients with hemodynamic dysfunction, 30-day mortality may be >15 % [8]. In the long term, chronic thromboembolic pulmonary hypertension (CTEPH) may increase the overall PE-associated mortality to >40 %. Factors which correlate with mortality in PE are age >70, malignancy, congestive heart failure, chronic lung disease, hypotension, tachypnea, and right heart dysfunction on echocardiography [7].

Risk Factors for VTE

General risk factors for VTE and PE include acute medical illness, immobilization, trauma, postoperative state, malignancy, age >65, obesity, metabolic syndrome, cigarette smoking, hypertension, oral contraceptives, hormone replacement, pregnancy, and inherited thrombophilias. A specific cause of VTE is frequently not found despite extensive evaluation. Pathophysiologically, inflammation, hypercoagulability, stasis, and endothelial injury underlie VTE risk.

In neurosurgical patients, a retrospective analysis of the American College of Surgeons NSQIP database comprising >1.7 million patients showed that ventilator dependence, immobilization, malignancy, chronic treatment with steroids, and sepsis were factors independently correlating with VTE [9].

Prevention of VTE in General

Mechanical and Medical Thromboprophylaxis

Intermittent compression devices (ICD) and/or medical thromboprophylaxis can be utilized for prevention of VTE in patients who are at risk, and several professional societies such as the American College of Chest Physicians (ACCP) have periodically published detailed guidelines on thromboprophylaxis [10]. The 8th edition of the ACCP guidelines was updated in 2012, and the recommendations from the current 9th edition were recently reviewed in detail [11]. There are several medications approved by the Federal Drug Administration (FDA) for thromboprophylaxis (unfractionated heparin, dalteparin, enoxaparin, rivaroxaban, fondaparinux, and warfarin), and the guidelines suggest approaches to thromboprohylaxis in specific patient populations and scenarios [11]. In general, ICD are used in isolation only in patients at risk for bleeding and, thus, ineligible for medical thromboprophylaxis. In some populations, e.g., patients with an active malignancy, the combination of ICD and medical prophylaxis may be more effective than either method alone [12].

The main concern limiting the use of medical prophylaxis in neurosurgical patients is hemorrhage. A meta-analysis of 30 studies including a total of 7,779 neurosurgical patients showed that ICD were superior to placebo in DVT prevention, and that low molecular weight heparin was superior to compression stockings [13]. Patients not treated with prophylaxis experienced a DVT rate of 15.5 %, and patients treated with ICD, unfractionated heparin, or low molecular weight heparin experienced reduced DVT rates of 1.9 %, 0.9 %, and 4.1 %, respectively [13]. In the majority of studies in this meta-analysis, medical thromboprophylaxis was administered prior to surgery, intraoperatively, or within the first 24 h postoperatively. Intracranial hemorrhage rates for patients receiving unfractionated heparin versus low molecular weight heparin were 0.35/1000 and 1.5/1000, respectively [13]. Caution should

be used in interpretation of any meta-analysis due to variability in study design of the included studies, and no conclusions should be drawn beyond that mechanical and medical prophylaxis reduced the rate of DVT formation in neurosurgical patients with medical prophylaxis incurring a relatively low, although perhaps not negligible, rate of intracranial hemorrhage.

Prevention of PE in the Setting of DVT

Anticoagulation

The first-line therapy for DVT and prevention of subsequent PE is systemic anticoagulation, which is discussed further in the section on treatment of PE.

While there is little controversy regarding anticoagulation for a proximal DVT, there are some nuances in the treatment of isolated distal DVT [11]. Distal DVT solely involves the veins of the calf, i.e., the peroneal, tibial, soleal, or gastrocnemius veins. The risk of embolization from distal DVT is generally lower than from a proximal DVT, but a distal DVT may extend proximally over time resulting in increased risk of PE [14]. If the patient does not harbor risk factors which correlate with DVT extension, the distal DVT may be followed with serial lower extremity ultrasonography, e.g., once every week for 2 weeks [11]. If the DVT does not extend during this time, the risk of subsequent expansion and/or embolization is thought to be low. If the DVT is observed to extend, anticoagulation should be commenced. Patients who are thought to be at high risk of distal DVT extension, however, should be anticoagulated [11, 14]. Factors correlating with extension include involvement of multiple veins, prior DVT/PE, active malignancy, or recent surgery or hospitalization.

Thrombosis of the upper extremity deep veins (subclavian, innominate, brachial, or axillary) may occur in patients with indwelling venous catheters. Anticoagulation is generally recommended for these patients [11].

Inferior Vena Cava Filters

There are currently two types of devices, permanent or retrievable filters, which can be inserted into the vena cava in order to prevent a piece of lower extremity or pelvic vein thrombus from lodging in the lung. While placement of an IVCF for this purpose makes intuitive sense, there are no studies in which patients were randomized to IVCF versus anticoagulation, and a Cochrane review failed to show support for the idea [6]. In the PREPIC trial, patients received anticoagulation with or without an IVCF [15]. In long-term follow-up, there was no mortality benefit of anticoagulation with IVCF versus anticoagulation without IVCF, but the rate of PE was initially lower (4.8 vs. 1.1 % at 12 days), while the rate of symptomatic DVT was higher at 2 years (20.8 vs. 11.6 %) with IVCF.

Due to the paucity of data, the indications for IVCF placement are diverse and vary among society guidelines [6]. While most agree that an IVCF is indicated in patients in whom anticoagulation is absolutely contraindicated, either temporarily or permanently, in order to decrease the risk of PE, some also advocate for IVCF placement in patients who had a recurrent PE despite therapeutic anticoagulation [16] and for other indications [6].

In patients in whom contraindications to anticoagulation are transient and/or the DVT is thought to have been caused by a temporary condition, retrievable filters can be used and subsequently removed [6].

Clinical Presentation of PE

There is a wide spectrum of presentations of PE, from no symptoms to sudden death, and some have observed that the majority of patients who die from PE do so before the diagnosis is made [8]. This observation requires that physicians should always have a high index of suspicion for PE when dealing with at-risk patient populations. Common symptoms and signs of PE include dyspnea, pleuritic chest pain, sinus tachycardia, as

well as local extremity symptoms and signs associated with DVT. Hemoptysis which is relatively specific for PE occurs only in approximately 10 % of patients, whereas lower extremity swelling which is relatively specific for DVT occurs in 42 % of patients [8].

Evaluation for PE

Clinical Probability

The evaluation for PE in hemodynamically stable patients is centered on the determination of clinical probability of PE. Several clinical scores of PE probability have been developed for this purpose. The Wells score and the revised Geneva score are frequently used (Tables 16.1 and 16.2).

Table 16.1 Wells score for PE in patients admitted to the hospital [17]

Clinical signs of DVT	3
Alternative diagnosis less likely	3
Prior DVT or PE	1.5
Heart rate >100 bpm	1.5
Recent surgery or immobilization	1.5
Hemoptysis	1
Cancer	1
Low probability: 0–1	
Intermediate probability: 2–6	
High probability: ≥7	
Dichotomized scoring	
PE unlikely: 0–4	
PE likely: >4	

Table 16.2 Revised Geneva score [18]

Heart rate >94 bpm	2
Pain on leg palpation and edema	1
Prior DVT or PE	1
Unilateral leg pain	1
Heart rate 75–94 bpm	1
Active malignancy	1
Surgery (GA) or fracture (LE)	1
Hemoptysis	1
Age >65 years old	1
Dichotomized scoring	
PE unlikely: 0–2	
PE likely: >2	

Once the clinical probability of PE is determined, further dedicated testing is done (Fig. 16.1). Blood testing for the fibrin degradation product, D-dimer, lower extremity compression ultrasound (CUS), and computed tomographic pulmonary angiography (CTPA) are currently frequently utilized in the evaluation of patients for PE.

D-Dimer

Depending on the specific assay used, a negative D-dimer result rules out acute VTE in most patients with low or intermediate probability of PE [7]. The D-dimer ELISA has a sensitivity of >93 % and specificity of 39 % and a high negative predictive value in the setting of low clinical probability of PE [7, 19]. D-dimer testing is less reliable in patients with conditions leading to an inflammatory response including traumatic injury, surgery, or pregnancy as well as in patients with high clinical probability of PE [7]. D-dimer levels may be above threshold in hospitalized patients and in individuals older than 65. Therefore, an elevated D-dimer level has a low positive predictive value and should generally be followed by CTPA. In summary, if clinical probability is low, a negative D-dimer rules out PE while an elevated D-dimer may warrant CTPA, while if clinical probability is high, only CTPA is indicated (Fig. 16.1).

Postoperative neurosurgical patients are expected to have an elevated D-dimer level due to causes other than VTE. One study prospectively evaluated D-dimer levels in 101 patients who underwent elective craniotomy primarily for tumors [19]. The D-dimer test used in the study used 0.5 mg/L as the normal cutoff, which had a 99.4 % sensitivity and a 38.2 % specificity for VTE in an outpatient population. In post-craniotomy patients, on day 3 postoperatively, patients without VTE had mean D-dimer levels of 1.59 mg/L, while those with VTE had mean D-dimer levels of 5.49 mg/L. The authors determined the value of 2 mg/L as a reasonable cutoff for VTE prediction with this particular test in postoperative patients who had undergone an elective craniotomy. The positive predictive value

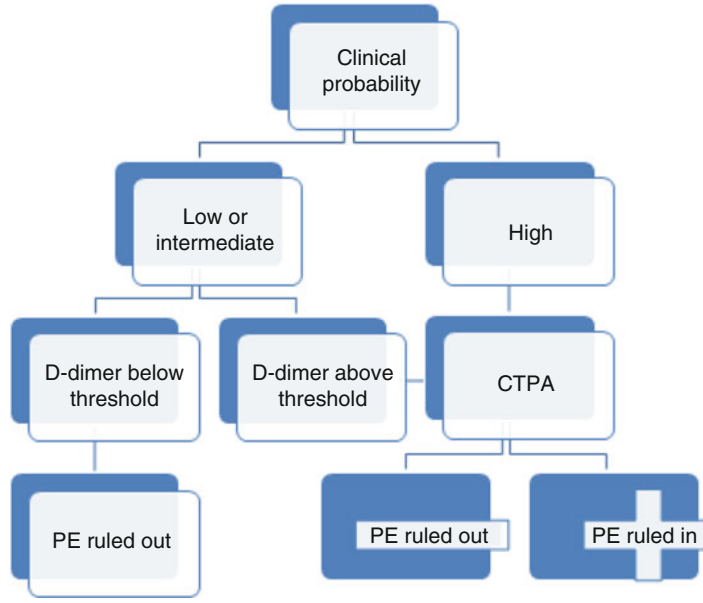

Fig. 16.1 Workup of PE based on clinical probability. *PE* pulmonary embolism, *CTPA* computed tomography pulmonary angiogram

was 73.2 %, and the negative predictive value was 95.6 %. In the study, patients who had a D-dimer level >4 mg/L were diagnosed with PE.

Imaging

Two invasive tests are considered the gold standard of PE and DVT diagnosis: conventional pulmonary angiography and venography, respectively. As these two tests are invasive, they are used only in highly selected patients, while non-invasive tests are utilized in the majority [7]. Although ventilation-perfusion scanning had been used in the past to make the diagnosis of PE, the high likelihood of a non-diagnostic scan (up to 50 %) has resulted in decreased use for the acute diagnosis of PE [8]. In the majority of cases, pulmonary CTPA has supplanted ventilation-perfusion scanning and compares favorably with invasive pulmonary angiography in the acute diagnosis of PE [7].

Since in patients with low clinical probability of PE a negative D-dimer effectively rules out a PE, CTPA is not indicated. Despite this, CTPA use has increased during the past decade, and a large percentage is being utilized in patients with low clinical probability of PE [20]. As part of the Choosing Wisely campaign, the goal of which is to identify and discourage tests or treatments that are used inappropriately in patients, the American Thoracic Society and the ACCP recommended that CTPA not be used in patients with low clinical probability due to unnecessary exposure to radiation and contrast. Additional consequences of performing CTPA in patients with low clinical probability of PE include incidental findings requiring additional tests and detection of small (sub-segmental) PE of unclear clinical significance.

In symptomatic patients with high clinical probability of PE, those with high D-dimer levels, and those with contraindications to CTPA, lower extremity CUS showing acute proximal thrombus is sufficient for diagnosis of PE [7]. CT venography is not routinely used in combination with CTPA due to concerns for radiation exposure and contrast load. Magnetic resonance pulmonary angiography and magnetic resonance venography have not replaced CTPA due to the high likelihood (approximately 52 %) of a non-diagnostic scan [7].

In hemodynamically unstable patients in whom CTPA may be impractical and/or unsafe, the clinical diagnosis of PE may be supported with findings on EKG (sinus tachycardia, right

bundle branch block, S1Q3T3) [21], bedside transthoracic echocardiography [TTE; right ventricular (RV) dysfunction (RV end-diastolic volume >30 mm; interventricular septal paradoxical motion and/or flattening; RV/LV ratio >0.9; pulmonary artery systolic pressure >30 mmHg; and tricuspid regurgitation] [4, 22], and/or CUS positive for acute thrombus.

Treatment of PE

Severity Score

Initial treatment of patients with PE begins with resuscitation and determination of disease severity [23]. Clinical prognostic models have been developed to estimate the risk of mortality in PE. The Pulmonary Embolism Severity Index (PESI) and its shortened version stratify patients into categories of risk of death by 30 days based on clinical variables [24, 25] (Table 16.3). Patients at high risk of death should be evaluated for thrombolysis and admitted to the hospital, while low-risk patients could conceivably be treated with anticoagulation as outpatients [7].

Table 16.3 PE severity index [24, 25]

Age >80 years/old	Age in years
Altered mental status	60
History of cancer	30
SBP <100 mmHg	30
heart rate ≥110 bpm	20
Respiratory rate ≥30 mmHg	20
Temperature <36 °C	20
PaO_2 <90 %	20
Male sex	10
History of heart failure	10
History of chronic lung disease	10
Class 1 ≤65 points	
Class 2 66–85 points	
Class 3 86–105 points	
Class 4 106–125 points	
Class 5 >125 points	
Dichotomized scoring	
Class 1 and 2: low risk	
Class 3–5: high risk	

Thrombolysis

Patients at high risk for death based on clinical score; presence of hemodynamic instability, RV dilatation, or dysfunction on TTE; and/or elevation of troponin or brain natriuretic peptide require rapid consideration of medical thrombolysis followed by systemic anticoagulation [26]. Some reserve medical thrombolysis for hemodynamically unstable patients with PE, but more recently medical thrombolysis, was suggested for patients with high risk of mortality who are hemodynamically stable and have a low risk of bleeding [26]. For example, a meta-analysis showed that hemodynamically stable patients with PE who exhibited RV dysfunction on TTE experienced a 2.29 times increase in short-term mortality [27].

Thrombolysis is most effective when administered within 48 h of onset, but retains some benefit for up to 14 days [4]. Contraindications to thrombolysis include recent trauma, bleeding, ischemic stroke, intracranial hemorrhage, major surgery, coagulopathy, or pregnancy [4]. Some have advocated thrombolysis despite the presence of contraindications after informed decision-making in moribund patients with massive PE [28].

Embolectomy

Patients with massive central PE at high risk of death in whom thrombolysis is contraindicated or those who have not responded to thrombolysis, i.e., those who continue to exhibit RV dysfunction, warrant consideration of surgical, or catheter embolectomy [4]. The goal of either procedure is to decrease clot burden in order to improve RV function. In the case of catheter embolectomy, catheter-delivered thrombolytic agents can further attenuate clot size [4].

Anticoagulation

Rapid anticoagulation is the mainstay of therapy in patients with PE. Decision-making regarding systemic anticoagulation focuses on determination of suitability for anticoagulation,

choice of drug, and length of therapy. Drugs currently approved by the FDA for the treatment of PE include unfractionated heparin, enoxaparin, dalteparin, fondaparinux, warfarin, and rivaroxaban (Table 16.4) [11].

Generally, prior to the availability of the novel oral anticoagulants (factor Xa inhibitors and thrombin inhibitors), the standard approach was to treat patients with PE with unfractionated heparin, enoxaparin, dalteparin, or fondaparinux followed by transition to a vitamin K antagonist with a target international normalized ratio (INR) of 2.0–3.0. For example, in a hypothetical patient with a history 2 weeks prior to a deep intracerebral hemorrhage due to hypertension presenting with a PE, anticoagulation with an intravenous unfractionated heparin drip as a bridge to warfarin is a reasonable treatment strategy given the short half-life of unfractionated heparin, as well as the complete reversibility of unfractionated heparin (with protamine) and warfarin (with vitamin K, prothrombin complex concentrates, or plasma) if the patient were to have recurrent bleeding despite adequate blood pressure control. Since two novel oral anticoagulant drugs, dabigatran etexilate and rivaroxaban, have been studied in the context of DVT and PE, and rivaroxaban is approved for use in this setting, a new therapeutic strategy for VTE has become available. Despite the ease of use of these drugs (unadjusted oral dosing, no routine laboratory monitoring, generally low hemorrhage risk in clinical studies), the lack of specific robust reversal strategies until recently limited their use in neurosurgical patients with DVT or PE in the acute postoperative or post-hemorrhage period. In October 2015, the FDA approved idarucizumab, a specific reversal agent for dabigatran etexilate. Future development of reversal strategies for the other novel agents may increase their utilization in patients at risk for hemorrhage, including neurosurgical patients.

Table 16.4 Drugs approved by the FDA for anticoagulation in VTE [11]

Drug Name	Dose	Monitoring
Unfractionated heparin	IV 80 U/kg bolus[a], then gtt	aPTT; goal 1.5–2.5
Enoxaparin	SQ 1 mg/kg q12h or 1.5 mg/kg q24h	
Dalteparin	SQ 200 U/kg q24h	
Fondaparinux	SQ, adjusted by weight	
Rivaroxaban	Oral 15 mg q12h for 21 days followed by 20 mg q24h	
Warfarin	Oral, titrated to INR	INR; goal 2.0–3.0

FDA Federal Drug Administration, *IV* intravenous, *U* units, *gtt* IV drip, *aPTT* activated partial thromboplastin time, *SQ* subcutaneous, *INR* international normalized ratio
[a]If intravenous unfractionated heparin is used in neurosurgical patients at a moderate risk for hemorrhage, the bolus dose may be avoided and slower anticoagulation commenced with the drip

Specific drugs may be preferred or avoided in certain conditions, for example, in patients with heparin-induced thrombocytopenia, heparins should be avoided; in patients with renal failure, low molecular weight heparins may accumulate; in patients with malignancy, heparins are preferred; and in pregnant patients, warfarin is contraindicated [10]. In neurosurgical patients at risk for bleeding in the setting of systemic anticoagulation, the treatment strategy and choice of drug should depend in part on the availability and effectiveness of agents for anticoagulant effect reversal.

Acutely, the goal of anticoagulation is active treatment, i.e., prevention of extension of the existing thrombus and embolization. Studies investigating different durations of treatment found that, in general, increased VTE recurrence was observed when anticoagulation was discontinued prior to 3 months, suggesting that 3 months is required to stabilize the thrombus [29]. There may be patients in whom a longer duration of treatment may appear reasonable, e.g., those with a large, proximal thrombus and a PE, but studies have not provided evidence that this is the case. Although some patients with small, distal thrombi which were provoked by a transient event such as surgery may not require the full 3-month treatment duration, it is reasonable to use 3 months as a guide given the uncertainty of the effects of shorter treatment durations. In summary, anticoagulation should be continued for 3 months after the index VTE, at which time determination of stopping therapy versus continuing indefinitely should be made [29].

After 3 months, the goal of anticoagulation changes from active treatment to prevention of subsequent new episodes of VTE. Decision-making centers on determination of the risk of new VTE versus the risk of hemorrhage: in patients with low risk of new VTE, anticoagulation should be stopped at 3 months, and in those at high risk, it should be continued indefinitely unless the risk of hemorrhage is higher [29]. The risk of recurrence of VTE depends on the factors that provoked the first episode. Transient, reversible factors such as surgery are associated with a 1 % VTE risk, whereas persistent factors such as active cancer may be associated with a rate as high as 20 %, within the year of anticoagulation discontinuation [29].

If the first VTE episode was unprovoked, D-dimer levels obtained 1 month after cessation of anticoagulation may aid in decision-making. Although the following results require confirmation, one study found that a woman with a negative D-dimer has a 5 % chance of VTE in the first year; a woman with a positive D-dimer, 10 %; a man with a negative D-dimer, 8 %; and a man with a positive D-dimer, 16 % [29]. Aspirin started after cessation of anticoagulation further decreases the risk of VTE recurrence in patients at low risk of recurrence [29].

Complications of VTE

Post-Thrombotic Syndrome

Post-thrombotic syndrome (PTS) typically affects the lower extremity and consists of edema, pigmentation, and ulceration [7]. While the syndrome is common—some state that it develops in up to half of patients with properly treated DVT—it is usually mild. Approximately 5–10 % of patients develop severe manifestations (ulceration) by 6 years after DVT [30].

Pathophysiologically, PTS is due to consequences of inflammatory damage to venous valves resulting in valvular reflux and, in combination with thrombus-related obstruction, venous hypertension [30]. A meta-analysis and a Cochrane review suggested that the use of elastic compression stockings (ECS) for up to 2 years after a proximal DVT may be effective at preventing the development of PTS [30]. Several other treatment modalities (surgical and procedural) are currently being investigated, but no firm recommendations can be made at this time.

Chronic Thromboembolic Pulmonary Hypertension

CTEPH develops in up to 4 % of patients with PE and is characterized by mean pulmonary artery pressure >25 mmHg 6 months after PE diagnosis. The main debilitating symptom is dyspnea which may occur at rest as well as with exertion. CTEPH is a risk factor for right heart failure and sudden death and, therefore, accounts for a percentage of PE-related mortality [7].

The main screening test for CTEPH is the ventilation-perfusion (VQ) scan, as, in contradistinction to the acute setting, CTPA is less sensitive than the VQ scan for chronic disease: VQ 96 % and CTPA 51 % [31]. In cases of suspected CTEPH based on screening, right-heart catheterization and conventional pulmonary angiography are necessary to properly assess risk/benefit of pulmonary endarterectomy, which is the recommended treatment for CTEPH [31]. Alternatives for CTEPH treatment including percutaneous approaches are currently being investigated, and no firm recommendations can be made at this time.

Patients who are not candidates for surgery, or patients in whom surgery did not eliminate pulmonary hypertension, may be candidates for medical therapy. Riociguat, a soluble guanylate cyclase stimulator, has been approved by the FDA for the treatment of pulmonary arterial hypertension and CTEPH specifically [32]. Additionally, lung transplantation may be an option in selected patients [31].

Summary

Neurosurgical patients are frequently at risk for VTE due to malignancy, immobility, and the post-surgical state. Testing for PE should be performed

based on the assessment of clinical probability of PE. Treatment options include systemic anticoagulation, thrombolysis, and/or thromboembolectomy with selection of specific treatments based on clinical severity. PTS and CTEPH are two potentially serious complications of VTE.

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