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CONTEMPORARY REVIEWS IN CRITICAL CARE MEDICINE

Pulmonary Embolism in the Critically Ill*

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Pulmonary embolism in the critically ill requires considerations beyond anticoagulant therapy. Measurements of chamber size by echocardiography and CT and of circulating biomarkers identify higher-risk patients with moderate accuracy and may aid determination of patient acuity. Preserving right ventricular function requires judicious use of volume administration, vasopressor, and perhaps vasodilator therapies. Obstructing thrombus can be treated with fibrinolytic drugs, percutaneous instrumentation, or surgically, but these treatments may not be equally effective or safe. Anticoagulant therapy in critically ill patients is likely best administered IV. Bleeding complications should be assiduously sought but do not necessitate anticoagulant discontinuation in every case. The antidotes protamine, desmopressin acetate, factor VIII inhibitory bypass activity, and recombinant factor VIIa may each have a place in controlling anticoagulant-related bleeding. The grave prognosis of heparin-induced thrombocytopenia warrants close surveillance, with rapid switching to lepirudin, argatroban, or fondaparinux necessary if it is suspected. Retrievable vena cava filters can be lifesaving, and at least one type may be safely removed after residence of nearly 1 year. ***(CHEST 2007; 132:313–324)***

Key words: anticoagulation; bleeding; critical care; heparin-induced thrombocytopenia; intensive care; pulmonary embolism

Abbreviations: aPTT = activated partial thromboplastin time; BNP = brain natriuretic peptide; CI = confidence interval; CTPA = contrast-enhanced multidetector helical CT pulmonary angiography; cTnI = cardiac troponin I; cTnT = cardiac troponin T; DDAVP = desmopressin acetate; DVT = deep vein thrombosis; HIT = heparin-induced thrombocytopenia; iNO = inhaled nitric oxide; IVC = inferior vena cava; LMW = low molecular weight; LV = left ventricular/ventricle; MPAP = mean pulmonary artery pressure; NT-proBNP = n-terminal pro-brain natriuretic peptide; PE = pulmonary embolism; RV = right ventricular/ventricle

Pulmonary embolism (PE) in critically ill patients is often massive, but the clot burden may not be the sole cause of hypotension. In this review, we primarily address management of the patient and, secondarily, the clot. Other excellent published reviews[1,2] taking different approaches are well worth reading. Important related topics, such as diagnosis of PE, will be included specifically in another review shortly to be published in *CHEST*. Updated American College of Chest Physician guidelines provide a graded summary of current clinical trial evidence for several aspects of PE management.[3]

Assessment of Right Ventricular Function

Right ventricular (RV) failure and low cardiac output presage mortality from PE. Early identification of these derangements might help save some of these critically ill patients by providing prognostic information, allowing stratification to more intensive surveillance and interventions. Imaging by echocardiography and spiral CT of the thorax and measurement of two classes of biomarkers, cardiac troponins and natriuretic peptides, have emerged as surrogate indicators for RV strain associated with adverse outcomes (Table 1). It is important to recognize that dichotomous decision making with these surrogate indicators relies on results from different cut points chosen by a variety of investigators, usually derived from retrospective case series.

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Table 1—*Imaging and Biomarker Findings Suggestive of Higher Risk in PE Patients*

Source	Subjects, No.	Diagnostic Finding	Outcome	Sensitivity, % (95% CI)	Specificity, % (95% CI)	Positive Predictive Value, % (95% CI)	Negative Predictive Value, % (95% CI)
Echocardiography							
ten Wolde et al,[4] 2004	310	RV dysfunction	Hospital mortality		58‡	5‡	
Kucher et al,[5] 2005	1035	RV hypokinesis	30-d mortality	52.4 (43.7–61.0)	62.7 (59.5–65.8)	16.1 (12.8–19.9)	90.6 (88.1–92.7)
Contrast-enhanced CT							
Schoepf et al,[8] 2004	454	RV/LV diameter > 0.9	30-d mortality	78.2 (65.6-87.0)‡	38.0 (33.3-43.0)‡	15.6 (11.8-20.3)‡	92.3 (87.0–95.5)‡
van der Meer et al,[9] 2005	120	RV/LV diameter > 1.0	PE-related 90 day mortality	100‡	45.1‡	10.1 (2.9–17.4)	100 (94.3–100)
Troponin							
Pruszczyk et al,[11] 2003	64	cTnT > 0.01 ng/mL	Hospital mortality	100 (62.9–100)	57.0 (44.1–69.0)	25.8 (13.9–42.6)	98.5 (87.0–99.8)
Mehta et al,[12] 2003	38	cTnI > 0.04 ng/mL	Cardiogenic shock	85.7 (48.7-99.3)	61.3 (43.8-76.3)	33.3 (16.3-56.3)	95.0 (76.4–99.7)
Punukollu et al,[13] 2005	33	cTnI > 0.04 ng/mL	RV dysfunction	66.7 (43.7-83.7)	73.3 (48.0-89.1)	75.0 (50.5-89.8)	64.7 (41.3–82.7)
BNP							
Pruszczyk et al,[11] 2003	79	NT-proBNP > 600 pg/mL	Hospital mortality	100‡	33‡	22.7‡	100‡
Kucher et al,[17] 2003	73	BNP > 50 pg/mL	Combined end point*	95 (76–99)	60 (47–72)	48 (33–63)	97 (81–99)
Combined testing							
Binder et al,[18] 2005	111	NT-proBNP > 1,000 pg/mL and RV dysfunction	Combined end point†	61.1 (38.6–79.7)	79.6 (70.3–86.5)	36.7 (21.9–54.5)	91.4 (83.2–95.8)
Scridon et al,[19] 2005	141	cTnI > 0.1 ng/mL and RV/LV diameter > 0.9	30-d mortality	60.7 (42.4–76.4)	75.2 (66.5–82.3)	37.8 (25.1–52.4)	88.5 (80.6–93.2)

*Combined endpoint of death, cardiopulmonary resuscitation, mechanical ventilation, vasopressors, thrombolytics, catheter fragmentation, surgical embolectomy.
†Combined end point of cardiopulmonary resuscitation, mechanical ventilation, vasopressors, thrombolytics.
‡Other values and CIs not reported.

Echocardiography

Massive PE is associated with RV enlargement (echocardiographic RV: left ventricular [LV] diameter ratio > 0.9),[4] RV free-wall hypokinesis with preservation of apical contractility, dilation of pulmonary arteries, and elevated RV systolic pressure (a surrogate for pulmonary artery systolic pressure). When RV dysfunction was present, short-term all-cause mortality and PE-related deaths were increased in the group with RV dysfunction compared to the group without RV dysfunction (11% vs 0.5%, respectively).[4]

From the International Cooperative Pulmonary Embolism Registry,[5] RV hypokinesis predicted an increased risk of death within 30 days in patients with a systolic systemic pressure > 90 mm Hg. After statistical adjustments, 30-day survival rates in patients with and without RV hypokinesis were 84% and 91%, respectively ($p = 0.001$). The relatively high survival despite RV dysfunction is noteworthy. Nonetheless, echocardiography can be used to identify which acute PE patients are at lower risk and requiring less intensive monitoring.

Contrast-Enhanced Multidetector Helical CT Pulmonary Angiography

Contrast-enhanced multidetector helical CT pulmonary angiography (CTPA) has become a common diagnostic tool for suspected PE and can provide prognostic information. CTPA was used to identify RV dilation in a group of patients with massive PE,[6] defined as patients with an RV:LV ratio > 1.5. RV and LV dimensions were measured by identifying a coronal slice estimated to show the maximal distance between the respective outer ventricular walls and the interventricular septum. The degree of RV dilation was found to correspond to the proximity and size of the PE. RV dilation on CTPA was present in 89% of patients with main pulmonary artery PE, 40% with lobar PE, 23% with segmental PE, and 17% of those with subsegmental PE.[7] The presence of RV dilation determined by an RV:LV ratio > 0.9 on CTPA was associated with an adjusted odds ratio for sudden death of 5.2 ($p = 0.03$) and overall 30-day mortality of 16%, compared to 8% in those with a ratio < 0.9.[8]

In a longitudinal CTPA study,[9] the association between mortality and increased RV:LV ratio > 1.0 persisted at 3 months, with a positive predictive value for PE-related mortality of 10% and a negative predictive value of 100%. Whereas changes in RV:LV ratio over time deserve more study, insufficient evidence exists at present to warrant serial CTPA examinations solely for that reason.[10]

Measurement of the RV:LV ratio from the chest CTPA in patients with PE appears worthwhile. Although the positive predictive value is low, chest CTPA can identify a set of patients without RV dilation at lower risk of complications and mortality, with a negative predictive value of at least 92%.

Laboratory Biomarkers

The cardiac biomarkers troponin and natriuretic peptide are potentially useful in managing patients with acute PE. There are no management studies to examine whether acting on these measurements changes mortality, but they can help identify patients who may benefit from intensive monitoring and further intervention.

Troponin: Cardiac troponin T (cTnT) and cardiac troponin I (cTnI) are specific to cardiac muscle and highly sensitive for cardiac myocyte injury. In one small series,[11] elevated cTnT identified a higher-risk group among normotensive PE patients; those with elevated cTnT had more severe RV dilation, higher end-diastolic RV:LV ratios by echocardiography (1.2 ± 0.26 vs 0.88 ± 0.24 [mean $\pm$ SD], respectively; $p = 0.0004$), and suffered all the deaths. Logistic regression analysis showed cTnT concentrations > 0.01 ng/mL had a marked impact on short-term prognosis (odds ratio, 21; 95% confidence interval [CI], 1.2 to 389).[11]

Another study[12] of patients with acute PE reported 47% with elevated cTnI levels (> 0.4 ng/mL) in whom the odds for the developing of cardiogenic shock was 9 (95% CI, 3 to 21). However, like other markers of myocardial necrosis, elevated cTnI levels may not persist despite persistent RV dysfunction. In a series of 57 consecutive normotensive PE patients,[13] cTnI was elevated in 48% of patients presenting ≤ 72 h after symptom onset (sensitivity of elevated cTnI for RV dysfunction by echocardiography, 67%; specificity,73%); but among the 42% of patients presenting > 72 h after acute PE symptom onset with echocardiographic RV dysfunction, none had elevated cTnI levels. Hence, unless cTnI is obtained early after acute PE symptom onset, it may not add reliable prognostic information.

B-Type Natriuretic Peptide: Brain (B-type) natriuretic peptide (BNP) is released from cardiac ventricular cells in response to high ventricular filling pressures and from coronary arteries. BNP and the N-terminal fragment of its prohormone, N-terminal pro-BNP (NT-proBNP), are indicators of increased cardiac wall stress and myocardial hypoxia.[14,15]

In one series,[16] serum NT-proBNP was elevated above normal reference values for age and sex in 83% of 79 consecutive patients with acute PE, in

only 50% of patients without echocardiographic RV dysfunction, but in nearly all with RV overload. Additionally, median NT-proBNP levels in massive PE were significantly higher than in submassive or nonmassive PE (9,865 pg/mL, 4,650 pg/mL, and 364 pg/mL, respectively).[16]

The accuracy of BNP for predicting critical illness (Table 1) complicating PE was explored for BNP values < 50 pg/mL, rather than the cutoff customarily used for diagnosing heart failure, 90 pg/mL.[17] Sensitivity, specificity, and positive and negative predictive values for the absence of critical illness were 95%, 60%, 48%, and 97%, respectively. This underscores that low BNP can help identify the lower-risk patient.

Combining Imaging and Laboratory Tests

In 124 consecutive PE patients, Binder et al[18] studied whether the combination of echocardiography to assess for RV dysfunction with either NT-proBNP or cTnT better predicted complicated in-hospital course or death. The negative predictive value of NT-proBNP < 1,000 pg/mL for absence of hospital complication and death was 95%, but values > 1,000 pg/mL had a positive predictive value for the combined outcome of only 25%. When echocardiography showing RV dysfunction was combined with NT-proBNP values > 1,000 pg/mL, the odds of the combined outcome was 12. Using echocardiography with cTnT > 0.04 ng/mL as a cutoff provided similar results. With a positive echocardiography results and either NT-proBNP > 1,000 pg/mL or cTnT > 0.04 ng/mL, the risk of severe complication or death was approximately 38%. In another study[19] evaluating the association of RV enlargement, elevated cTnI, and 30-day risk of all-cause death in patients with PE, the mortality rate for patients with cTnI > 0.1 ng/mL was 32%, with RV enlargement 28%, and for patients with both findings, 38%.

How best to use these imaging and biomarker data (Table 1) in PE patients is unproven, but risk evidence suggests that severe, continued, or worsening findings warrant close observation even if deterioration is not otherwise clinically apparent. The shorter half-life of BNP or NT-proBNP compared to troponins suggests the former tests may be better to follow over time (*eg*, 12 hourly) in unstable patients.[20] What degree of worsening requires additional intervention is uncertain. Physicians caring for PE patients should obtain this information on a case-by-case basis and consider higher acuity care when findings identify a patient at substantial risk.

RV Resuscitation

When PE impairs RV function, further possible consequences include low cardiac output and shock and myocardial ischemia due to poor coronary perfusion pressure and diastolic overdistension. Enlarged right-sided chambers can push the septae into left-sided chambers, limiting their diastolic filling and interfering with systolic contractile function. While each PE patient's heart is different due to a different preexisting extent of cardiopulmonary disease, some practices have evolved reflecting sensible physiologically based management.

Volume Administration

The use of judicious volume infusion in resuscitating the RV has been shown to improve cardiac output in PE patients with decreased RV preload. While provision of adequate RV preload is essential for cardiac output, overdistension of the RV with volume resuscitation can impair coronary perfusion and LV filling, diminishing LV output. In a report[21] of a small series of patients with acute PE and a cardiac index < 2.5 L/min/m^2, treatment with 500 mL of dextran significantly increased cardiac index from a mean of 1.6 to 2.0 L/min/m^2. Continuous cardiac output pulmonary artery catheters allowed the calculation of RV end-diastolic index; patients with low values had a greater improvement with fluid therapy.[21] Currently, an author of that report (A. Mercat, MD; personal communication; June 2006) uses echocardiography in underperfusing PE patients to guide fluid crystalloid infusion until the RV:LV diastolic diameter ratio appears to be 1.0. The RV is then considered adequately filled, and IV dobutamine and norepinephrine are added as needed. "Prophylactic" early intubation with positive pressure ventilation is avoided because of its potential interference with RV preload.

Vasopressors

There are no human trials comparing vasopressors in acute PE. In a canine model, Hirsh et al[22] demonstrated that norepinephrine was superior to phenylephrine in increasing cardiac output and RV coronary blood flow, although both agents similarly improved mean arterial BP.

Vasodilator Therapies

Since nitric oxide is a mediator in multiple pathophysiologic pathways during PE (hypoxic vasoconstriction, platelet activation, and endothelin and thromboxane release), there is a physiologic rationale for its use to lower pulmonary artery pressure and

unload the RV. An early report[23] of inhaled nitric oxide (iNO) administered at a dosage from 10 to 15 ppm was followed by a subsequent report[24] of dosages from 12 to 27 ppm, carefully titrated in individual patients. In both pig and dog models, iNO decreased mean pulmonary artery pressure (MPAP) from 10 to 20% with no change in systemic BP.[25] In a review[25] of human data, there was a 17 to 47% decrease in MPAP after administration of 5 to 20 ppm iNO administered via the inhalation arm of the ventilator circuit. This therapy merits further investigation including outcome studies. It may become a management cornerstone for temporizing or definitively unloading a pressure-overloaded RV to allow time for recovery.[26]

Sildenafil, an inhibitor of phosphodiesterase that leads to increased cyclic guanosine monophosphate, also causes pulmonary artery vasodilation. In a dog model[27] of large PE, IV sildenafil lowered MPAP up to 8 to 16 mm Hg. In a single case report,[28] physicians administered 50 mg of sildenafil po to a patient with deterioration due to PE and the MPAP decreased from 56 to 46 mm Hg, with a rise in cardiac index from 2.1 to 3.2 L/min/m^2. This agent shows promise as another potential therapy to lower MPAP to support a failing RV.

Relieving Pulmonary Artery Obstructing Thrombus

Infused Thrombolytic Therapy

Thrombolytic (also called fibrinolytic) therapy is indicated in patients with shock due to PE and perhaps as follows: (1) in patients deteriorating despite aggressive medical therapy, and (2) normotensive patients with evidence of RV impairment. The latter two indications are debated.[29] Contraindications include active internal bleeding, history of cerebral hemorrhage, recent intracranial or intraspinal trauma or surgery, intracranial neoplasm, arteriovenous malformation or aneurysm, known significant bleeding diathesis, and severe uncontrolled hypertension.

Thrombolytic therapy is relatively uncommonly used. Among 108 patients (4.5% of patients in the registry) with massive PE (defined as systolic BP < 90 mm Hg) from the International Cooperative Pulmonary Embolism Registry,[30] only 33 patients received IV thrombolytic therapy. Recurrent PE by 90 days occurred at similar rates (12%) in those who did and did not receive IV thrombolysis, as did death (46% and 55%, respectively; $p = 0.44$), but major bleeding (22% vs 9% respectively, $p < 0.001$) and intracranial bleeding (3% vs 0.3%, respectively; $p < 0.001$) were both more common among thrombolysis recipients. Although recipients and nonrecipients of IV thrombolysis had important differences with respect to clinical characteristics, this registry provides a snapshot of real-world thrombolysis utilization.

For PE, thrombolytic therapy has generally been administered by peripheral IV infusion rather than directly in a pulmonary artery after a persuasive multicenter clinical trial[31] showed no superiority of the latter. Current advocates of clot-directed thrombolysis in the pulmonary arteries claim that newer techniques that include clot fragmentation with the infusion give superior results to those of prior infusion studies.[32] Reports of the newer technique do not describe decreased bleeding, an oft-cited rationale for locally infused thrombolysis.

In head-to-head comparisons, thrombolytic drugs show similar results.[33] Some experts believe the less fibrin-specific agents (*ie*, activators of plasmin in all body fluids) first developed (streptokinase, urokinase) establish a fibrinolytic state with less bleeding risk; others believe more fibrin-specific drugs (activators of plasmin where fibrin is already bound, *eg*, at blood clots) such as alteplase, reteplase, and tenecteplase are preferred for their clot specificity. Dosages of common thrombolytic drugs are presented in Table 2.

Whether a thrombolytic drug improves survival of a patient in cardiac arrest is uncertain. A multinational trial in cardiopulmonary resuscitation patients is underway, but placebo-controlled pilot studies have shown a higher rate of return of spontaneous circulation and perhaps survival after a bolus of either 50 mg of tenecteplase[34] or 50 mg of recombinant tissue plasminogen activator (alteplase).[35]

Table 2—*IV Thrombolytic Therapy for PE*

Drugs	Dosing	Comment*
Streptokinase	250,00 U over 30 min; then 100,000 U/h for 24 h	Approved regimen; may increase bleeding risk
	1.5 million U over 60 min	This rapid regimen is unapproved[65]
Urokinase	4,400 U/kg over 10 min; then 4,400 U/kg/h for 12 h	
Alteplase	10-mg bolus; then 90 mg over 2 h	

*For each thrombolytic drug, IV unfractionated heparin is begun after the infusion is completed and aPTT is less than two times the control value.

Percutaneous Catheter Devices

In patients with RV failure and a large, central embolic burden, the concept of mechanically reestablishing pulmonary blood flow with percutaneous devices is appealing. None of the available devices has regulatory agency approval for PE or has been tested in randomized controlled trials of PE patients. Embolus suction devices and fragmentation devices are designed to relieve obstruction by disrupting a central clot and allowing it to disperse to more peripheral, smaller vessels, where the larger pulmonary arterial cross-sectional area allows a reduction in pulmonary artery pressure despite partial occlusion by clot fragments. These techniques may also enlarge the surface area of the clot, improving the efficacy of fibrinolytic medications. When a pigtail rotational fragmentation catheter was used in addition to thrombolytic therapy in patients with PE obstructing $> 50\%$ of the pulmonary artery and a ratio of heart rate to systolic BP > 1, the ratio improved early but a significant MPAP decrease was not noted until 48 h.[36]

The AngioJet catheter (Possis Medical; Minneapolis, MN) aspirates thrombus after macerating with a high-pressure saline solution jet. In a case series[37] of 17 patients, 2 died, 1 from massive PE, and 1 from unclear etiology. Severe hemolysis with resulting anemia and resulting pancreatitis have been described as complications of this device. Of the 15 patients who survived to 24 h, 13 were alive at 18 months (2 were unavailable for follow-up).

Surgical Embolectomy

Surgical embolectomy had been reserved for patients with massive PE and hemodynamic instability and historically was accompanied by a high mortality rate (30%).[38] However, a better 2-year experience with surgical embolectomy[39] reported 29 patients who underwent the procedure, most due to contraindications to thrombolytic therapy and two for progressive hypotension and hypoxemia despite thrombolytic therapy. Twenty-six patients (89%) survived, attributed to careful selection prior to cardiovascular collapse and use of a beating-heart technique. Major lessons claimed from this experience included the importance of routine placement of inferior vena cava (IVC) filters, not operating on patients with out-of-hospital cardiac arrest without restoration of spontaneous circulation, avoiding operating on octogenarians, and avoiding aortic cross-clamping. A subsequent report[40] of 3-year survival of a larger group of 47 patients was 83%. Another report[38] employing careful patient selection and surgical therapy prior to cardiovascular collapse reported 92% survival. However, surgical embolectomy on cardiopulmonary bypass with the heart in arrest has also been used for rescue of patients remaining unstable despite IV thrombolytic therapy. In a series of patients[41] in whom thrombolysis failed for major PE who either received repeat IV thrombolysis or underwent surgical embolectomy, the latter group had significantly fewer recurrent PEs and a trend toward fewer deaths. Taken together, these studies suggest surgical embolectomy in expert centers has an important role in PE treatment in selected patients with failing aggressive medical therapy or in whom it is contraindicated. It has been recommended that each center develop a protocol for local management (*eg*, with percutaneous or surgical embolectomy) in such patients.[42]

Antithrombotic Treatment: Drug Choice and Dosage

The great success of anticoagulant drugs in preventing death from PE suggests they may also play a role in preventing embolization of existing clot, but there is no mechanism-based evidence for this. Some anticoagulants may favorably affect patients with deranged pathophysiology, improving ventilation-perfusion relationships. For example, positive airway pressure applied to PE patients treated with unfractionated heparin appeared to result in greater lung expansion than that found in patients not yet treated with heparin.[43] Anticoagulant drugs also increase bleeding and the seriousness of bleeding in patients who do bleed.

If evaluation of a critically ill patient leads to suspicion of PE, prompt assessment of bleeding risk should ensue. Only rarely is anticoagulant treatment flatly contraindicated (*eg*, active hemorrhage in the brain or another vital organ, uncontrolled bleeding threatening tissue perfusion); but in those situations, consideration of prompt placement of a vena cava filter (see below) and clot removal (see above) should be undertaken. When the absolute contraindication remits, if a relative contraindication is present, anticoagulant therapy can be started, perhaps without a bolus and at somewhat lower intensity, in our opinion. There are multiple evidence-based methods to assess the probability of pulmonary embolism in a patient[44,45] but no fail-safe formula, so the decision to begin anticoagulant treatment based on suspicion is always a clinical one, best made after bedside evaluation.

Absent an important contraindication, prompt administration of sufficient anticoagulant is best current practice. Undertreatment (*eg*, failure to prolong the activated partial thromboplastin time [aPTT] to therapeutic range) increases risk of treatment fail-

ure.[46] Completed clinical trials being prepared for publication make clear that the same dosage of anticoagulant may be sufficient to provide protection against recurrence in patients presenting with deep-vein thrombosis (DVT) yet fail to prevent recurrence in PE patients. This result supports previous evidence that unfractionated heparin is cleared from plasma more rapidly in PE than DVT[47]; hence, higher dosages may be required for PE. We support early administration of sufficient anticoagulant with subsequent dosage reduction if appropriate, rather than a strategy of "creeping up" to therapeutic dosing. Starting dosages of different anticoagulants for PE treatment of critically ill patients are presented in Table 3. Not all these treatments are necessarily equally effective (or in clinical trial terminology, noninferior) to one another. There are few trials directly comparing these drugs. Clinical trials for regulatory approval of new anticoagulants understandably enrolled relatively few critically ill patients for three valid reasons: (1) such patients are uncommon among PE patients; (2) clinician-investigators were reluctant to randomize their sickest patients to unproven therapy; and (3) patients requiring extraordinary interventions (drug, catheter, or other thrombolysis or vena cava filters) were excluded from the clinical trials.

Moreover, uncertainty exists regarding the subcutaneous dosing route for critically ill patients with PE. Subcutaneous low-molecular-weight (LMW) heparin prophylaxis leads to lower plasma drug levels, measured as anti-factor Xa activity, in surgical ICU patients with or without shock than in more stable patients on a surgical ward[48] despite use of an identical dosing scheme. Many physicians select the Table 3 anticoagulants with IV treatment regimens, rather than subcutaneous ones, for critically ill PE patients.

Monitoring Antithrombotic Treatment

Table 4 presents estimated therapeutic ranges for assays of anticoagulant treatment. The greatest experience exists for unfractionated heparin, whose level is measured by the aPTT. Urgent results from this assay must be rapidly and reliably available in hospitals in order to minimize the risk to a critically ill patient of undertreatment or overtreatment. Dosing by actual (rather than ideal) body weight[49] is recommended. Frequent (every 4 to 6 h) aPTT monitoring in critically ill patients will allow heparin dose titration according to published algorithms while both assisting understanding of complications and informing future treatment. For patients with bleeding complications not sufficiently serious to absolutely contraindicate continued anticoagulant treatment, reducing the dosage to obtain a somewhat shorter aPTT prolongation and treatment of the bleeding site can be sufficient to allow continued effective anticoagulant treatment of severe PE.

"Heparin resistance" refers to failure to prolong the aPTT to a therapeutic range despite a higher than usual infusion dosage of unfractionated heparin. A randomized clinical management trial[30] of patients with this problem compared raising the dosage of infused heparin until the aPTT was elevated to the therapeutic range, to weight-based heparin dosages, monitored with anti-Xa level rather than an aPTT target. That study[50] showed efficacy outcomes were similar for both groups despite receipt of 30% more heparin in the group whose infusions were titrated to achieve "therapeutic" aPTT prolongation. Bleeding was more frequent in this latter group. Because these patients are uncommon, it was impossible for the investigators to enroll sufficient patients to confidently exclude inferior efficacy outcomes in the "underdosed" group. Nonetheless, it is clinically

Table 3—*Appropriate Starting Dosages of Anticoagulants for PE in Critically Ill Patients**

Drugs	Dosages	Comments
Unfractionated heparin	80 U/kg IV bolus; 18 U/kg/h IV; titrate by aPTT	Avoid with HIT; dose by actual body weight
Fondaparinux	Subcutaneous qd; 5 mg if < 50 kg, 7.5 mg if 50 to 100 kg, and 10 mg if > 100 kg	Not tested in well-hydrated patients with creatinine levels > 2 mg/dL; no reliable monitoring
Enoxaparin	Subcutaneous, 1 mg/kg q12h	Uncertain whether to "cap" dosage > 120 kg or 150 kg; reduce to 1 mg/kg q 24 h for calculated creatinine clearance < 30 mL/min
Dalteparin	Subcutaneous, 200 U/kg q24h	120 U/kg and 100 U/kg q12h have also been used; insufficient evidence in renal insufficiency
Tinzaparin	Subcutaneous, 175 U/kg q24h	Evidence exists for dosing by weight without "capping" and for standard dosage if calculated creatinine clearance > 20 mL/min
Lepirudin	0.1 mg/kg/h IV, no bolus; follow aPTT	Not the approved labeled dose, which is higher, includes a bolus, and is associated with increased bleeding
Argatroban	2 μg/kg/min IV, no bolus, follow aPTT	Final dosage is often lower

*Some anticoagulants approved in certain countries are not included in this Table.

Table 4—*Therapeutic Ranges of Injected Anticoagulants in Critically Ill PE Patients*

Drugs	Range	Comments
Unfractionated heparin	aPTT range corresponding to anti-Xa level of 0.3 to 0.7 U/mL	Each laboratory should identify the proper aPTT range for the heparin, assay kit and device
Fondaparinux	Usually not monitored	Conventional anti-Xa assays may overestimate dosage, even when fondaparinux is used to create the standard curve
Enoxaparin	Usually not monitored	Therapeutic range uncertain; 4-h (peak) desired anti-Xa level is 0.6 to 1.0 U/mL; trough level desired is > 0.4 U/mL
Dalteparin	Usually not monitored	Therapeutic range uncertain; for q12h dosing, similar to enoxaparin; for q24h dosing, 4-h anti-Xa level 1.0 U/mL, trough > 0.4 U/mL
Tinzaparin	Usually not monitored	Once-daily dosing 4-h peak target level is 0.85 anti-U/mL, trough > 0.4 U/mL
Lepirudin	aPTT 1.5 to 2.5 times control value	aPTT values in the lower part of the range may be less prohemorrhagic and equally effective; ensure prolonged overlap with oral anticoagulant and normalization of platelet count for HIT
Argatroban	aPTT 1.5 to 3 times control value and < 100 s	Ensure prolonged overlap with oral anticoagulant and normalization of platelet count for HIT

reasonable not to uptitrate unfractionated heparin in such "heparin-resistant" patients for whom anti-Xa monitoring is available, and instead use the weight-based regimen, so long as the anti-Xa level is in the range of 0.35 to 0.7 U/mL during steady-state infusions.

Two other anticoagulants approved for IV treatment in heparin-induced thrombocytopenia (HIT) are the thrombin inhibitors lepirudin (an irreversible inhibitor) and argatroban (a reversible inhibitor). Although the approved labeling for lepirudin describes a therapeutic aPTT prolongation range of 1.5 to 2.5 times the laboratory normal median value, subsequent experience with excessive hemorrhage has led some experts[51] to recommend reducing the dosage; these latter recommendations are presented in Table 3. The aPTT is also recommended for identifying the target infusion rate of argatroban, with recognition that on transition to a vitamin K antagonist such as warfarin, the international normalized ratio target is 3 to 4, rather than 2 to 3, due to an increment provided by the argatroban. Without evidence for their efficacy in PE, these two drugs should be avoided in critically ill patients unless there is concern for HIT (see below). An advantage of lepirudin in patients with liver disease is its renal elimination. Since argatroban is eliminated by the liver, its dosage is independent of renal function, except that renal insufficiency generally increases bleeding risk. A disadvantage of lepirudin is that antibodies develop frequently after an average of 5 days, paradoxically enhancing its anticoagulant activity.[52]

Reports of IV administration of LMW heparins are limited to normal volunteer and periprocedural percutaneous coronary intervention studies; there are none for PE or DVT treatment. Subcutaneous dosing in critically ill patients is probably best administered every 12 rather than every 24 h for enoxaparin and dalteparin. For tinzaparin, only once-daily dosing data are available. For fondaparinux, dosing is once daily due to its longer terminal half-life (approximately 15 h) than that of the LMW heparins. Anti-Xa levels can be checked for LMW heparins (peak approximately 4 h after dosing; trough just before the next dose); target levels are presented in Table 4. Fondaparinux levels are imprecisely measured by the conventional anti-Xa assays, but ICU patients were included in the fondaparinux PE treatment trial. [53] in which noninferiority to unfractionated heparin was reported. LMW heparins and fondaparinux both undergo renal elimination, so accumulation can be expected with decreased renal perfusion. Early attainment of therapeutic levels without monitoring is the advantage of LMW heparins and fondaparinux. However, prolonged anticoagulant activity if bleeding complicates treatment and uncertainty about absorption after subcutaneous injection in critically ill patients are concerns that lead the authors to prefer IV unfractionated heparin therapy (in the absence of HIT) with close aPTT monitoring and dosage adjustment for critically ill PE patients.

Complications of Antithrombotic Treatment

Bleeding: Disturbed physiologic homeostasis (*eg*, renal insufficiency, hepatic insufficiency, stress ulceration, hemodilution of plasma clotting factors, thrombocytopenia, disseminated intravascular coagulation, postoperative state) predisposes toward bleeding, the most common complication of anticoagulant treatment. Surveillance for and early response to bleeding in critically ill patients can prevent serious and fatal complications. Surveillance includes frequent monitoring of hemoglobin or he-

matocrit, examination for physical evidence of bleeding, and investigation of whether bleeding could be contributing to other abnormalities (*eg*, hypotension, abdominal distension, obtundation). When serious bleeding is suspected in a critically ill PE patient receiving anticoagulant therapy, several nearly simultaneous interventions should take place: institution of frequent monitoring for bleeding (*eg*, hemoglobin measurements every 2 h), control of the bleeding site if that can be managed, administration of depleted blood components (*eg*, fresh frozen plasma, packed RBCs, platelets), volume expansion if indicated, consideration of an anticoagulant antidote, and discontinuation of anticoagulant administration.

If tolerable, volume expansion with frequent measurement of blood hemoglobin will help assess whether bleeding is continuing, accelerating, or abating. Gastric stress ulceration can often be successfully controlled endoscopically, whereas control of diffuse pulmonary and intracerebral hemorrhage is difficult. When significant blood loss occurs, clotting factors will be depleted although common global tests such as the aPTT and prothrombin time may be normal or only slightly elevated, and clotting factors in the form of fresh frozen plasma should be administered despite lack of ready proof of their depletion. Crystalloid administration alone or with albumin reliably lowers the concentration of circulating clotting factors, likely impairing hemostasis. Decisions regarding RBC and platelet transfusions are clinical ones, dependent on assessment of oxygen delivery to vital tissues and platelet levels and function, respectively. Prompt implementation of these measures with rapid and repeated assessment distinguishes intensive from usual hospital care.

The optimal use of antidotes in anticoagulant-related bleeding continues to evolve. Protamine sulfate is regularly used as an antidote to unfractionated heparin in cardiothoracic surgery, where it can cause hypotension, pulmonary hypertension, and decreased cardiac output in that setting. Nonetheless, it is an effective but uncommonly used antidote for unfractionated heparin. It should be dosed at 1 mg of protamine sulfate per 100 U of unfractionated heparin to reverse the latter. The half-life of infused unfractionated heparin is approximately 60 min, so protamine infusion >3 h after heparin infusion is stopped may not be helpful. Protamine is less helpful in reversing LMW heparin-related bleeding because it appears to reverse $<40\%$ of anti-Xa activity, the primary anticoagulant activity of these compounds.[54] This may vary with the LMW heparin used, depending on its degree of sulfation. LMW heparins, eliminated renally, have extended half-lives (4 to 8 h in normal subjects after subcutaneous administration) compared to unfractionated heparin and may require repeated protamine dosing, at 1 mg protamine per 1 mg or 100 U of LMW heparin estimated to be remaining in the patient.

Desmopressin acetate (DDAVP) is a synthetic analog of vasopressin altered from the parent molecule to remove vasopressor activity (antidiuretic activity remains) and provide a longer duration of effect (6 to 24 h rather than 2 to 6 h).[55] It is widely available in hospital pharmacies. DDAVP, administered by IV infusion at 0.3 μg/kg actual body weight, increases plasma factor VIII and von Willebrand factor by up to four times within an hour, with the effect sustained (depending on consumption) for up to 12 h. Tachyphylaxis may occur after three to four doses at 12-h intervals. DDAVP improves platelet aggregation[55] and reduces blood loss not only in bleeding episodes of von Willebrand disease but in the impaired hemostasis accompanying renal insufficiency, cardiac, and noncardiac surgery. Side effects are minimal, and hypercoagulability has not been reported. In patients without platelet disorders, its effect is discernible but relatively modest (*eg*, approximately 10% reduction of blood loss in cardiac surgery). DDAVP deserves consideration in PE patients with bleeding complications as a safe, inexpensive, and readily available hemostatic agent but is unlikely to provide definitive management.

Prothrombin complex concentrates for infusion have been used to control hemorrhage in nonhemophiliac patients. They are sold inactivated in Europe and elsewhere but not in the United States; only one activated concentrate, factor VIII inhibitory bypass activity, is available in the United States, approved for use only in hemophiliac patients with factor VIII or IX inhibitors. There is no evidence to support the use of factor VIII inhibitory bypass activity in bleeding patients without such inhibitors. Inactivated prothrombin complex concentrates are being used to counteract overanticoagulation with vitamin K antagonists like warfarin and in cases of life-threatening bleeding.[56] Unlike fresh-frozen plasma, they are quickly administered, being easily reconstituted and not requiring blood typing or thawing. They are followed promptly with 5-mg IV injections of vitamin K and fresh-frozen plasma. Their efficacy in patients anticoagulated with inhibitor drugs like heparin or with life-threatening bleeding without coagulation factor depletion requires further study.

Recombinant factor VIIa, indicated for hemophiliac patients with inhibitors, is being more widely used to control hemorrhage in a variety of patients, including those with intracerebral hemorrhage.[57] The risk of thrombosis appears increased compared to placebo but is relatively small. The disadvantage of this agent of high expense should be balanced against its life-saving potential in critically ill bleeding pa-

tients. The best dosage is uncertain; 90 μg/kg, repeated in 2 h if needed, is approved for hemophiliac patients with bleeds, but lower dosages (*eg*, 50 μg/kg by infusion) have been used in patients bleeding from other causes (*eg*, trauma, warfarin-related bleeding). The thrombotic risk, while low (25 per 10,000 infusions), may be similar to or higher than that of factor VIII inhibitory bypass activity.[58] This agent has been shown to partially reverse inhibition of thrombin generation by the newer pentasaccharide generation of injected antithrombotics, such as fondaparinux.[59]

HIT: Often, the diagnosis of HIT is provisional, complicated by the delayed return of an assay, limited positive predictive value and sensitivity, and because cardinal signs of the syndrome, arterial and/or venous thrombosis, are already present in the patient. Moreover, a drastic reduction in platelet count $< 100{,}000/\mu L$ is not required for the disease to be present; a reduction to 50% of peak platelet count appears sufficient in postoperative patients.[60] HIT is most commonly precipitated by unfractionated heparin administration (average 4% incidence), so most PE patients are at risk, and less commonly by LMW heparins. Fondaparinux induces the HIT antibody but does not provoke the disease, which is caused by generalized platelet activation and mediated by antibodies to an altered conformation of platelet factor 4 induced by unfractionated and LMW heparin administration. Not all patients with these antibodies developing will have this pathologic complication, but its mortality rate remains 15% and amputation rate is 6% with best approved treatment. Early recognition is believed to be important. Since both unfractionated heparin and LMW heparin are implicated, they must be stopped immediately and fondaparinux (not approved), lepirudin, or argatroban, substituted. If the patient has recently received warfarin, vitamin K should also be administered.[61] One of these injected anticoagulants should be continued until thrombosis is improving and the platelet count returns to normal or baseline. At that time but not before, warfarin transition may be initiated.

IVC Filter

Discontinuing therapeutic anticoagulation in a patient with critical PE is a grave consideration but is required in the face of major, particularly uncontrollable bleeding. An IVC filter inserted from the femoral, jugular, or basilic vein may be life-saving. A retrievable filter can be removed in the future if the patient can be stabilized. The indications for IVC filter are an absolute contraindication to, or complication of, anticoagulation in patients with proximal vein thrombosis.[3] In a case series of surgical pulmonary embolectomy, IVC filter has been attributed benefit.[39] In a large observational study,[62] the use of an IVC filter was associated with a 2.6-fold increase in the likelihood of being rehospitalized for venous thrombosis at 1 year.

In the only long-term randomized study of filter placement in prevention of PE after proximal DVT, there was a nonsignificant decrease in the occurrence of PE at 2 years,[63] and a 63% reduction in risk of PE at 8 years ($p = 0.008$); the cumulative incidence decreased from 15 to 6%.[64] There were significantly more DVTs in the filter group at both 2 years and 8 years but no difference in mortality. In selected high-risk patients with proximal DVT, use of an IVC filter may be indicated, but not routinely. Removable filters are attractive, but in the Prevention du Risque d'Embolie Pulmonaire par Interruption Cave study,[64] 33% of the patients with an IVC filter and 50% of the patients without an IVC filter had PE 2 to 8 years following the original DVT. Length of filter therapy and the subgroups that benefit the most from these devices are still unknown. Emerging evidence shows some filters can be removed after as long as 350 days.[65]

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