CLINICAL MANAGEMENT STRATEGIES FOR PATIENTS WITH DEEP VEIN THROMBOSIS AND PULMONARY EMBOLISM

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Under-recognition of venous thromboembolism (VTE), which is gaining attention as a problem in the general population, is of grave concern in the intensive care unit (ICU). Because many critically ill patients are at higher risk for VTE, optimal approaches regarding diagnosis, treatment and thromboprophylaxis must receive high priority.

Venous Thromboembolism in Trauma Patients

Venous thromboembolism occurs in approximately 1 in 1,000 patients a year in the United States, and trauma patients are particularly susceptible. "This is important because about 28% of trauma survivors, who are usually younger patients, will go on to develop recurrent venous stasis syndrome within 20 years," said Lena M. Napolitano, MD, FCCM, from the University of Michigan, in Ann Arbor.

The incidence of VTE without prophylaxis is as high as 80% after major trauma. Despite this increased VTE risk, up to 25% of trauma and surgical patients fail to receive VTE prophylaxis (*J Trauma*. 2007;62:557). Despite the association of surgery with VTE risk, nearly 20% of surgical patients fail to receive VTE prophylaxis. Even more troubling are data showing that up to 50% of total hip and total knee replacement patients–a population already at high risk because of older age–do not receive prophylaxis for VTE. (Tsai et al. *Arch Intern Med*. 2002;162:1182; Clagett, Reisch. *Ann Surg*. 1988;208:227; Clagett et al. *Chest*. 1998;114 [suppl 5]:531S)

"I think we're all well aware of the fact that hip and extremity fracture, major trauma, and spinal cord injury are high on the list of risk factors for VTE in the hospital setting," said Napolitano. In studying VTE prevention in trauma patients, Knudson et al identified several risk factors for developing deep vein thrombosis (DVT) after trauma: age older than 30 years, pelvic fractures, spine fractures with paralysis, coma, immobilization for more than 3 days, lower extremity fractures, direct venous injury, injury severity score (ISS) of 16 or higher, large transfusion requirements, and presence of femoral venous catheters (Knudson et al. *J Trauma*. 1994;37:480).

According to the 2002 Eastern Association for the Surgery of Trauma (EAST) Practice Management Guidelines for the Prevention of Venous Thromboembolism in Trauma Patients, high risk for DVT among trauma patients, as supported by existing evidence, involves the presence of two risk factors for post-traumatic VTE: spinal fractures and spinal cord injury (Rogers et al. *J Trauma*. 2002;53:142). Older age is considered an additional risk factor, but it is not clear at what age the risk increases substantially.

The importance of providing thromboprophylaxis to trauma patients was underscored by a Canadian prospective study. Geerts et al looked at 716 patients to determine their baseline rate for presence of DVT; none of the patients had received prophylaxis (Geerts et al. *N Engl J Med*. 1994;331:1601). They used serial impedance plethysmography and lower extremity contrast venography; the latter was adequate in only 349 patients. The investigators detected DVT and pulmonary embolism (PE) in 58% and 1% of the 349 patients, respectively. Among patients who had multisystem injuries and did not receive DVT prophylaxis, the rate of DVT ranged from 38% to 77%. "This was a pivotal study that alerted us to the high baseline rate of DVT among trauma patients," remarked Napolitano.

Geerts went on to conduct a study of VTE prophylaxis in trauma patients (Geerts. *N Engl J Med*. 1996;335:701). Patients were randomized to receive low-dose unfractionated heparin (UFH) or low-molecular-weight heparin (LMWH) consisting of enoxaparin 30 mg twice daily. "The results were striking, showing that low-molecular-weight heparin was more effective than low-dose heparin in preventing DVT after trauma," said Napolitano. The rates of total DVT (occurring above and below the knee) were 44% among patients receiving low-dose UFH versus 31% for those receiving LMWH. Proximal DVT occurred at rates of 15% with low-dose UFH and 6% with LMWH.

"These results, published in 1996, changed the tide of our therapy for DVT prophylaxis in trauma patients, and they mirrored the data in hip fracture and orthopedic surgery," Napolitano said. She noted the high rates of VTE and mortality from PE associated with hip fracture surgery (see Table 1). "We also now recognize that the risk of developing DVT doesn't end when patients are discharged from the hospital. It actually continues for a period of well beyond a month."

Table 1. VTE and Hip Fracture Surgery

	Rate of VTE without prophylaxis		
	% DVT rate	% PE rate (range)	
		Any PE	Fatal PE
Total hip replacement	45-57	0.7-30	0.1-0.4
Total knee replacement	40-84	1.8-7.0	0.2-0.7
Hip fracture	36-60	4.3-24	3.6-12.9

DVT: deep vein thrombosis; PE: pulmonary embolism
Geerts et al. *Chest*. 2001;119:1325

The pathophysiology explaining the high risk of VTE among trauma patients is based on Virchow's triad: increased hypercoagulability, increased stasis and vascular damage. All aspects of this triad can be disrupted in cancer, trauma (including surgery), and pregnancy. Factors that can lead to stasis include paralysis and immobilization. Those that lead to endothelial damage include venous trauma and fractures. Hypercoagulability is related to severity of injury by ISS score and also by multiple transfusions (Knudson et al. *J Trauma*. 1994;37:480).

"The balance between the physiologic thrombus needed to prevent blood loss in the injured patient and the development of pathologic intervascular thrombus and thrombosis is a delicate one," she said. "The prothrombotic state that results from trauma usually tips this balance in favor of more–rather than less–thrombus, through the inhibition of fibrinolysis. That's one of the mechanisms by which we actually have an increased thrombogenic state in trauma." While this mechanism enables the patient to survive the injury rather than bleed to death, it also encourages VTE development, particularly in the presence of other risk factors.

The spectrum of VTE ranges from pulmonary embolism to DVT. "It really is a continuum," said Napolitano. "A number of studies have shown that about 50% of patients who have proximal DVT in the leg have concurrent asymptomatic PE. Conversely, DVT (primary asymptomatic) has been found in about 80% of patients with PE." Other findings show that 90% of patients with demonstrated PE after orthopedic surgery also had DVT (Girard et al. *Chest*. 1999;116:903).

Napolitano closed her presentation by emphasizing that trauma is one of the highest risk factors for DVT and PE and that prophylaxis is very important. Trauma patients should receive low-dose UFH or LMWH, unless anticoagulant therapy is contraindicated. Foot pumps (sequential compression devices) have been used extensively, but there are minimal data on this approach. "They have the same problem as pneumatic compression devices and have been shown to stay in place only 50% to 75% of the time," she said. In terms of removable or retrievable inferior vena cava (IVC) filters, new methods of placement are now available, but an IVC filter should be reserved for patients who have a clear contraindication to anticoagulation.

Diagnosis and Treatment of Pulmonary Embolism

"Most ICUs don't routinely screen for DVT or PE, but the data make us wonder if perhaps we should," said Victor F. Tapson, MD, from Duke University Medical Center, Durham, North Carolina. The problem of underdiagnosis of pulmonary embolism in ICU patients is evidenced by autopsy data that revealed 20% to 27% of ICU patients had undetected PE (Neuhaus et al. *Chest*. 1978;73:460; Moser et al. *JAMA*. 1981;246:1422). More recent postmortem studies also show that PE is one of the most commonly missed major diagnoses among critically ill patients.

The diagnosis of VTE among ICU patients is challenging because of the complexities of critically ill patients, who often present with multiple disease processes. Hypotension and hypoxemia, for example, are common in the ICU patient population and may be attributed to sepsis, acute respiratory distress syndrome (ARDS), congestive heart failure, pneumonia, or other disorders, while VTE may not even be considered. Sedation and paralysis also contribute to the difficulty of VTE diagnosis because symptoms cannot be reported, although asymptomatic DVT probably is more common in the ICU patient population.

These and other complexities also impact the diagnostic approach. One approach that has limitations, but may be appropriate to use sometimes, is the ventilation/perfusion (VQ) scan. The VQ scan usually is nondiagnostic in ICU patients because of the high incidence of abnormal chest radiographic results among ICU patients. The Prospective Investigation of Pulmonary Embolism Diagnosis (PIOPED) study noted that VQ scanning results were inconclusive for 90% of patients with chronic obstructive pulmonary disease and 77% of patients with cardiopulmonary disease (Division of Lung Diseases, National Heart, Lung, and Blood Institute. *JAMA*. 1990;263:2623). Despite the drawbacks of VQ scanning, an international study is re-examining the possibility that it may be useful in some situations.

"I think we have to suspect PE in critically ill patients, and when we do, we're probably not going to do D-dimer testing because it often isn't helpful in this population. So we're going to do an imaging study," stated Tapson. Computed tomography (CT) is a better choice in the ICU than VQ scanning. "However, the worsening renal insufficiency IV contrast becomes contraindicated, precluding CT," noted Tapson. "Transport of the patient for imaging studies also is a frequent issue concerning critically ill patients."

Studies have shown that measurement of the right ventricle (RV)/left ventricle (LV) ratio using helical CT angiography (CTA) in patients who have PE appears to be worthwhile (Reid et al. *Clin Radiol*. 1998;53:694; Sukhija et al. *Cardiology*. 2005;103:156; Schoepf et al. *Circulation*. 2004;110:3276; van der Meer et al. *Radiology*. 2005;235:798). Although the positive predictive value is low, CTA can identify a set of patients without RV dilation who are at lower risk of complications and mortality, with a negative predictive value of at least 92%.

"If the right ventricle is abnormal when we do a CT scan–and sometimes that's an incidental finding–we should seriously suspect PE," said Tapson. "Also, we need to keep in mind that abnormalities in RV size and function will impact our choice of therapy. Providing a thrombolytic agent in the patient with an enlarged right ventricle is at best controversial," he stated. Other tests, such as leg ultrasound, also may be ordered to make an indirect diagnosis of PE.

In terms of treatment, the American College of Chest Physicians (ACCP) recommends that patients with a high clinical suspicion of PE receive anticoagulation therapy while awaiting the outcome of diagnostic tests (Buller et al. *Chest*. 2004;126[suppl 3]:401S). "This is an important recommendation," said Tapson. "In the ICU, we're frequently concerned about bleeding problems because our patients often are at higher risk of having low platelets. However, if we think the risk of bleeding is low, we should consider initiating anticoagulation therapy when we have a high suspicion for PE. Usually we get a diagnosis within a couple of hours, but sometimes a couple of hours can make a difference."

For treatment of confirmed DVT or nonmassive PE, LMWH is recommended rather than UFH. The advantages of LMWH over UFH include increased bioavailability, once or twice daily subcutaneous delivery versus intravenous administration, lack of the need for monitoring in most situations, and lower incidence of heparin-induced thrombocytopenia (HIT).

The treatment of massive PE in the ICU is especially problematic. "We often have a good idea when massive PE is present because it results in hemodynamic instability and hypotension, but deciding what to do about it is not always so simple," stated Tapson. Carlbom and Davidson recently reviewed the important considerations regarding treatment of PE in critically ill patients (Carlbom, Davidson. *Chest*. 2007;132:313). Some of these concerns include the potential for bleeding with the use of anticoagulant therapy and the need to preserve RV function, requiring the judicious use of volume administration and vasoactive therapies.

The correlation between severity of massive PE and mortality was studied by Wood (Wood. *Chest*. 2002;121:877). The results showed that RV failure accounted for death among most patients who had massive PE. "The RV cannot pump against high resistance," said Tapson. "When PE impairs RV function, possible consequences include low cardiac output and shock and myocardial ischemia due to poor coronary perfusion pressure and diastolic overdistention. Enlarged right-sided chambers can push the septum into the LV, limiting diastolic filling and interfering with systolic contractile function."

Tapson briefly reviewed findings from studies that reported on recurrent PE and mortality in trials comparing the use of thrombolytic agents with heparin for the initial treatment of PE. He noted that these were all small studies, and a larger international study is under way. "I hope we'll learn whether the mortality rate is improved among patients who have acute PE and RV dysfunction when they receive thrombolytic therapy," he said.

Data on vasodilator therapy indicate that while a potential benefit exists, these agents usually are not used in acute PE. "We do have data showing that nitric oxide and sildenafil can help patients with chronic PE and pulmonary hypertension, but pure vasodilator therapy in acute PE is not used," remarked Tapson. Inodilators such as deputamine may be considered, but this is based on few data.

The development of HIT is an important issue to address. "HIT is a clotting disorder, not a bleeding disorder, and it can develop in patients with platelet counts above 100,000," he said. Platelet transfusion can increase thrombosis. Simply stopping heparin may not prevent thrombosis, but it must be done. Warfarin is contraindicated as acute monotherapy because of the potential for acute protein C depletion. "It's important to refrain from starting warfarin too soon, before the patient's platelet count is up." he said. Both lepirudin and argatroban therapy have been associated with effective anticoagulation and platelet recovery. While HIT appears to be much more common with standard heparin, it may also occur with LMHW.

In summary, Tapson reiterated the need to have a high suspicion of DVT or PE in the critically ill patient. "We know VTE is a common problem in the ICU, and that it's difficult to diagnose." CT scanning is probably the best modality to use (when possible), while D-dimer testing has little value in ICU patients and VQ scanning may be helpful in patients with minimal cardiopulmonary disease. Anticoagulant therapy should be started when there is high suspicion for PE and low bleeding risk. Fluids should be considered, and vasopressors can be given as needed in the presence of hypotension. "The use of thrombolytics in ICU patients remains problematic, but certainly hemodynamically compromised patients who have hypotension should be considered for thrombolytic therapy."

VTE Prophylaxis in the Critically Ill Patient

In a report of a critical analysis of patient safety practices for hospitalized patients released by the Agency for Healthcare Research and Quality (AHRQ), appropriate use of thromboprophylaxis in at-risk patients was listed as the number one recommendation (AHRQ. Prevention of VTE After Injury. Available at www.ahrq.gov/clinic/epcsums/vtsumm.htm). "Ironically, despite the fact that critically ill patients are the sickest in the hospital, VTE has been a silent problem in the ICU," said Deborah J. Cook, MD, from McMaster University in Hamilton, Ontario, Canada. "We know many pulmonary emboli are underdiagnosed in the ICU," she said.

According to data from a study on failed UFH prophylaxis, the incidence of VTE among ICU patients is approximately 10% (Cook et al. *Crit Care Med*. 2005;33:1565)."Of course, this rate is higher among subgroups of patients at even greater risk," she said.

DVT and PE acquired in the ICU tend to occur during the first seven to 10 days of arrival to the unit. The clinical importance of the site of the clot in VTE may be very relevant. "We don't have data about how to or whether to treat distal DVT in the ICU setting, but most clinicians would concur that proximal DVT is possibly or probably more clinically important," stated Cook.

In discussing prophylaxis approaches, Cook first addressed mechanical prophylaxis (e.g., antiembolic stockings and various pneumatic devices). "The rationale for using mechanical approaches to minimize the propensity to develop thrombi is compelling," remarked Cook. By decreasing venous dilation, increasing blood flow velocity, improving valvular cusp function, and increasing fibrinolysis, mechanical prophylaxis reduces venous stasis, venous endothelial injury, and hypercoagulability.

"Despite this rationale, results from studies of antiembolic stockings fall short of what we would ideally like to make strong recommendations," said Cook. "The data are sparse, of only modest quality, and primarily involve surgical patients," explained Cook. She also noted that if too tight, the stocking may induce superficial thrombosis. Furthermore, the Centers for Disease Control and Prevention (CDC) is addressing a possible role of these stocking as fomites. Because of the absence of clear benefit, the potential for harm, and poor compliance, these stockings are not used routinely.

Similar problems have been observed with pneumatic compression devices (PCDs). Results from more than 30 randomized controlled trials (RCTs) evaluating the use of these devices in a heterogeneous patient population revealed problems regarding discomfort, uncertain or poor compliance, cost, and lack of availability.

In evaluating mechanical thromboprophylaxis in ICU patients, including trauma patients, 13 observational studies found no differences between mechanical modes (e.g., antiembolic stockings or pneumatic devices) and either heparin or control therapy. However, two RCTs found an increased incidence of DVTs in patients receiving PCDs compared with those receiving LMWH (Limpus et al. *Am J Crit Care*. 2006;15:402). "The authors noted, however, that the stockings were used inappropriately, and although mechanical devices are widely used, few RCTs exist to guide practice," Cook said.

The mainstay of VTE prophylaxis is heparin therapy. The efficacy of perioperative heparin therapy in reducing fatal PE and VTE has been documented. "In contrast, the benefit of heparin in medical patients has been debated," said Cook.

Data on heparin dosing was evaluated in a systematic review of RCTs using unfractionated heparin 2 or 3 times daily in heterogenous medical populations (King et al. *Chest*. 2007;131:507). While direct comparisons between the twice versus thrice daily dosing regimens could not be made, an indirect comparison showed that major bleeding risk was significantly higher in the patients receiving heparin more frequently. "Since the thrice-daily heparin did not show a statistically significant reduction in VTE and suggested more bleeding, we do not have strong data to support that regimen," noted Cook.

The potential interaction between cessation and commencement of prophylactic heparin and administration of activated protein C (APC) has captured great clinical and research interest. "We know that in patients with severe sepsis, activated protein C is not sufficient for thromboprophylaxis. The addition of heparin is needed, if it is determined to be safe in that patient," Cook said, emphasizing that the patient's bleeding risk should be evaluated carefully each day. If heparin is contraindicated in any patient, mechanical approaches may be suitable.

Cook briefly discussed VTE prophylactic practices across the globe. Survey results indicate that ICU directors in Canada use UFH routinely and reserve LMWH for high-risk (e.g., trauma) patients, while those in France favor the routine use of LMWH agents. Clinicians from both countries report infrequent use of mechanical approaches, except when heparin is contraindicated. In Australia and New Zealand, clinicians primarily use UFH, although LMWH is used in high-risk patients.

Tapson et al recently reported on the International Medical Prevention Registry on Venous Thromboembolism, known as IMPROVE (Tapson et al. *Chest*. 2007;132:936). "The registry, which includes data on more than 15,000 patients in 52 hospitals, shows that medical patients are not receiving thromboprophylaxis with heparin as they should," said Cook. Other data reveal that when UFH is used, the dosing usually is twice daily.

The use of LMWH for VTE prophylaxis in patients with renal insufficiency has been troubling to clinicians, because of the bioaccumulation associated with it. The concern is that serial injections of LMWH in the presence of renal insufficiency might result in elevated levels of anti-activated factor X (Xa) that do not return to the baseline level. A sustained elevation in anti-Xa level increases the risk of bleeding. Unfortunately, evidence relating anti-Xa levels to clots and bleeding is sparse.

"We don't know whether we should or not give LMWH prophylaxis to patients with renal insufficiency." Data from a meta-analysis of studies using treatment doses of enoxaparin in patients with severe renal insufficiency suggest that bleeding rates may be lower if the doses are adjusted for renal insufficiency (Lim et al. *Ann Intern Med*. 2006;144:673).

A more recent study, co-investigated by Cook, examined the effects of the LMWH dalteparin prophylaxis on the anti-Xa levels of medical and surgical ICU patients with severe renal insufficiency (Spencer et al. *Arch Intern Med*. 2008;168:425). Severe renal insufficiency was defined as a creatinine clearance less than 30 mL/minute. "We know that when creatinine clearance is less than 30 mL/minute, that level may rise and fall," said Cook. "Many patients with creatinine clearances less than 30 mL/minute are able to urinate and are not on dialysis; some are receiving intermittent renal replacement therapy. When we measured trough anti-Xa levels, we saw no evidence of bioaccumulation." In addition, among the few patients who had detectable trough anti-Xa levels, no correlation was made with VTE or bleeding. "It may be that in patients with renal insufficiency, treatment doses of LMWH may bioaccumulate, but prophylactic doses of LMWH do not appear to bioaccumulate."

In closing, Cook noted that audits reported in the literature indicate the use of heparin in VTE prophylaxis is increasing. "That's the good news," she said. "The bad news is that while the tide is changing, many informal audits that are not published demonstrate the under-utilization of thromboprophylaxis in ICU patients. We know we still have challenges ahead to optimize prophylaxis, which will primarily involve anticoagulant agents."

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Continuing Education Self-Assessment

CLINICAL MANAGEMENT STRATEGIES FOR PATIENTS WITH DEEP VEIN THROMBOSIS AND PULMONARY EMBOLISM

5. Which of the following diagnostic studies for VTE is likely to be the best choice for the patient who has moderate pulmonary disease?
   a. CT scan
   b. D-dimer test
   c. VQ scan

6. Evidence is robust that in patients with renal insufficiency, anti-Xa levels remain high with prophylactic doses of low-molecular-weight heparin.
   a. True
   b. False

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