CONGRESS REVIEW

38th Critical Care Congress
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Continuing Education Information

Learning Objectives

At the conclusion of this activity, participants should be able to:

- Evaluate the implications of developing delirium in the ICU
- Assess the risk factors and prevention techniques for various ICU patient populations
- Describe the new pharmacological options for management of delirium in the ICU
- Assess the benefits of pre-mix total parenteral nutrition solutions in the ICU
- Discuss the risks of caloric deficit in ICU patients and the benefits of supplemental parenteral nutrition
- Discuss results of a 2008 international nutrition survey, with a focus on success or failure in nutrition delivery
- Identify the clinical problems presented by thromboembolic disease in the ICU
- Assess the therapeutic options for deep vein thrombosis and pulmonary embolism in the ICU with emphasis on the newer agents
- Evaluate the controversial areas of management

Target Audience

This continuing medical education offering is intended to meet the needs of any healthcare provider involved in the care of critically ill patients, including advanced practice nurses, critical care nurses, intensivists, critical care fellows, anesthesiologists, internists, surgeons, cardiologists, pulmonologists, emergency medicine practitioners, neurologists and respiratory therapists.

Type of Activity

This activity will focus on increasing knowledge-based content. It is presented as summaries of live activities, followed up with a few questions for self-assessment.

Competencies

SCCM supports recommendations that will promote lifelong learning through continuing education. SCCM promotes activities that encourage the highest quality in education that will enhance knowledge, competence or performance in critical care practice. This activity will meet the following:

- Practice Applications
- Communication
- Quality Improvement

Evaluations and CE/CME Applications

To apply for credit and evaluate the course, visit www.sccm.org/2009ConRev
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Physicians/Physician Assistants

SCCM designates this educational activity for a maximum of 1.5 *AMA PRA Category 1 Credits*™. Physicians should claim credit commensurate with the extent of their participation in the activity.

Nurses

SCCM is approved by the California Board of Registered Nursing, Provider No. 8181, and approves this activity for 1.5 contact hours.

Pharmacists

SCCM is accredited by the Accreditation Council for Pharmacy Education (ACPE) as a provider of continuing pharmaceutical education. This activity will provide 1.5 continuing education hours (236-000-09-230-H01-P).

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UPDATES ON THERAPEUTIC OPTIONS FOR DVT AND PE PREVENTION AND MANAGEMENT IN THE ICU

Critically ill and injured patients clearly are at high risk for venous thromboembolism (VTE), yet autopsy studies reveal that this condition is underdiagnosed in the intensive care unit (ICU). It is crucial that intensivists identify patients at greater risk for developing VTE and stay abreast of current and emerging preventive and therapeutic interventions.

Thromboembolic Disease in the Critically Ill: What Is the Risk?

Deborah J. Cook, MD

A 2004 survey, conducted by the Canadian Critical Care Trials Group, indicated that intensivists do not rely solely on traditional deep venous thrombosis (DVT) features to implement prophylaxis.[1] They are not dissuaded from providing prophylaxis by the absence of symptoms or physical signs in critically ill patients because they are rarely present in this population. Furthermore, most intensivists said they considered even small thrombotic events to be of concern given the poor cardiopulmonary reserve of intensive care patients.

"So why is VTE so often underdiagnosed in our ICU patients?" asked Deborah J. Cook, MD, from McMaster University in Hamilton, Ontario, Canada. Many factors converge to increase the risk of VTE in the intensive care patient. Baseline VTE risk among ICU patients can be conceptualized as increasing according to the type of patient subset. "We know that orthopedic and trauma patients have a very high risk of VTE, while general medical and surgical patients are at moderate to high risk," she explained. "Obviously, the acute illness and the duration of conditions that induce immobility – such as spinal cord injury – are also very important. And, of course, being critically ill or injured is in itself a risk factor."

Other DVT risk factors among the critically ill population relate to baseline patient characteristics, such as personal or family history of DVT or pulmonary embolism (PE) and presence of end-stage renal disease. In addition, specific ICU events and exposures, including administration of vasopressor agents and platelets, place the patient at higher risk.

Ten Reasons to be Concerned about VTE in the ICU

- Intensivists are best trained to provide the best ICU care.
- Critically ill patients are at high risk.
- Unrecognized DVTs can progress to PEs.
- VTE is common on autopsy of decedents.
- History and physical exams are not enough to diagnose VTE.
- Biomarkers don't diagnose VTE.
- ICU patients have poor cardiopulmonary reserve.
- VTE confers risk of morbidity and mortality.
- VTE consumes healthcare resources.
- ICUs are the "last frontier" for prophylaxis.[9]

Autopsy studies reveal a high degree of VTE underdiagnosis, particularly among populations outside North America (it is important to note that this does not mean these populations have more cases of VTE, only that more post-mortem examinations are conducted). According to Cook's summary of the evidence, there is a 20% to 60% discordance between clinical and autopsy diagnoses. In 20% to 40% of these cases, the autopsy findings would have changed the patient's treatment. In five studies, PE was the most commonly missed diagnosis.

"The clinical silence of DVT in the ICU is an important concern," Cook said. "It severely attenuates our ability to identify these events during physical examination." DVT remains clinically silent in the ICU for several reasons. Leg examinations are overlooked because more focus is placed on the cardiopulmonary systems. Even if the lower limbs are examined, unilateral leg swelling – a sign of DVT – is rare in critically ill patients, as they are recumbent. One study found that 95% of DVTs in ICU patients are not clinically suspected, noting that detection through physical examination is difficult in critically ill patients.[2] In addition, risk stratification screening and diagnosis using a d-dimer biomarker cannot be relied upon in this population.[3]

"We know that there are patients who have VTE when they come into the ICU – these are the so-called prevalent cases," stated Cook. "A few studies have identified that either DVT or PE is present on admission, though most of the time it is not clinically suspected." The prevalence of DVT among medical-surgical patients has been reported to be 2% to 4% upon ICU admission.

Research suggests that DVTs occur early in ICU stays. One study found a 24% incidence of DVT among 110 patients receiving mechanical ventilation for less than one week.[4] The occurrence was approximately four times greater in lower limbs than upper limbs.

Just how much of a problem do VTE events pose to intensive care patients? "This is difficult to determine," Cook said. "We don't have great data on this." She described an unmatched case-control study conducted by her group that crudely compared the clinical consequences of DVT among patients with prevalent or incident DVT versus those with no DVT.[5] "The results suggested that DVT may be associated with a longer ICU and hospital length of stay and perhaps a higher rate of mortality. However, these unrefined comparisons tend to inflate the attributable morbidity and mortality rates." Studies that use matching methods and large databases are needed.

One of the biggest risk factors for DVT in intensive care patients is the lack of thromboprophylaxis. The literature contains only a few randomized controlled studies that evaluate heparin thromboprophylaxis among medical-surgical ICU patients. Cook discussed four studies that compared placebo versus unfractionated heparin, placebo versus low-molecular-weight heparin (LMWH), or unfractionated heparin versus low-molecular-weight heparin (LMWH). The results of the placebo-controlled trials showed that for every five to seven patients receiving prophylaxis, one VTE event is prevented (see Table 1).

Data from self-report observational studies show a trend that thromboprophylaxis utilization in ICUs is increasing.[6] "This is very good news if it is reflective of what's happening around the world," noted Cook. "It's especially important now that we know VTE prevention is a top patient safety initiative in many jurisdictions."

Table 1. RTCs of Heparin Thromboprophylaxis in Med-Surg ICU Patients

Reference	Population	Diagnosis	Control Rate	Intervention Rate	NNP
Cade 1982	119 general ICU patients	Fibrinogen leg scanning	Placebo 29%	UFH 5000U bid 13%	6
Kapoor 1999 (abstract)	791 MICU patients	DUS on day 1 and q3 daily	Placebo 31%	UFH 5000U bid 11%	5
Goldhaber 2000 (abstract)	325 MICU patients	DUS on days 3,7,10,14	UFH 5000U bid 13%	Enoxaparin 30mg bid 16%	–
Fraisse 2000	223 COPD patients ventilated ≥48h	Venogram by day 21	Placebo 28%	Nadroparin ~ 70AXa U/kg q daily 15%	7

NNP, number needed to prophylax; DUS, duplex ultrasonography; UFH, unfractionated heparin

The risks involved with administering prophylaxis in the form of LMWH prophylaxis include the potential bioaccumulation of the drug in patients with renal insufficiency and a risk of increased bleeding. In discussing these concerns, Cook noted findings from a multicenter observational study conducted by the Canadian Critical Care Trials Group.[7,8] ICU patients who had a creatinine clearance of >30 mL/min (and were either receiving or not receiving dialysis) were administered once-daily dalteparin for 30 days or until discharge from the ICU. Twice weekly researchers measured trough and serial anti-Xa levels and measured bleeding daily. "We found no problems with excessive bleeding," Cook said. "We also demonstrated that the drug is absorbed, and we did not identify any bioaccumulation." Large, rigorous studies of LMWH are needed to clarify its risk profile. "We then should compare it with unfractionated heparin and determine if and when dose adjustments are indicated."

Controversies: What is the Role of Thrombolytic Therapy and IVC Filters?

Kenneth E. Wood, DO, FCCM

"For years, controversy has been surrounding thrombolytic therapy, and we still run the gamut of opinion related to its utility and approach," stated Kenneth E. Wood, DO, FCCM, from the University of Wisconsin Hospitals & Clinics in Madison.

According to Wood, the literature has been handicapped by a pervasive view of dividing clots into massive and submassive, based on anatomic size. "The reality is that the vast majority of patients who present with an anatomically massive clot do not have hypotension. I encourage you to risk stratify pulmonary embolism and establish the threshold for thrombolytic therapy by defining severity as the integration of clot size and underlying cardiopulmonary status."

A large clot with good cardiopulmonary architecture and a very small clot with poor cardiopulmonary architecture will present similarly; both demonstrate the same physiologic characteristics. In either case the presence of shock or hemodynamic instability defines failure of the physiologic compensatory mechanisms and is associated with a high mortality, which necessitates either the use of thrombolytic therapy or if contraindicated, surgical embolectomy. It is underappreciated that 30% of PE patients with cardiac arrest will survive which warrants consideration of the use of thrombolytic therapy in cardiac arrest when the pre-test probability is high or emergent surgical embolectomy, despite the absence of a confirmed diagnosis preoperatively. Equally underappreciated, the mortality rate is nearly zero among patients with a non-dilated right ventricle who receive anticoagulation therapy.

Hypotension is a major risk factor. In looking at the physiology, a differentiating feature has been the inability to maintain compensatory perfusion pressure gradients (shock) or a systolic blood pressure less than 90 mm Hg. As is true in other disease states, coldness of the extremities is a bad sign. "In pulmonary embolism, the mortality is increased five- to seven-fold with the inability to maintain compensatory forward flow or shock," said Wood.

The unambiguous and proven benefits of thrombolytic therapy are clear. "We have unequivocal data demonstrating the rapidity of clot thrombolysis as measured by every metric, with almost every hemodynamic measurement uniformly improving shortly after thrombolysis," said Wood. "Similarly, speculative data suggest a decrement in the recurrent embolism and the chronicity of pulmonary hypertension. Decreased mortality is probably the most ambiguous benefit to date."

The physiologic and anatomic benefits of thrombolytic therapy occur during the acute, early phase. "But as you get out to day five, virtually every study has shown that the extent of the clot resolution is no different between heparin and thrombolytic therapy at that point," Wood said.

Wood said he believes we are moving closer to liberalizing the thrombolytic threshold. The recommendations of the American College of Chest Physicians (ACCP) concur with this observation.[10]

Wood also noted the dramatic rise in using inferior vena cava (IVC) filters. Clinical data demonstrate the benefit of IVC filters in patients with DVT. One randomized controlled trial comparing the use of an IVC filter versus LMWH or unfractionated heparin found a PE incidence of 1.1% with the IVC filter and 4.8% with heparin on day 12.[11] When the study follow-up was reported at two years, no change in PE incidence was noted, yet a significant increase in DVT incidence was seen for the IVC group (20.8%) compared with the heparin groups (11.6%).

"Data now have been reported for up to eight years," Wood said (see Table 2). "There was a significant decrease in PE incidence, but the price paid for that was a significant increase in DVT incidence." The results also revealed that, regardless of whether an IVC filter or heparin was administered, 70% of patients with DVT developed post-thrombotic syndrome – even those who did not develop a PE.[12] "This highlights, more than anything else, the need for prophylaxis," Wood stressed.

Another frequently cited trial revealed results that conflict with the above-mentioned data. In a retrospective study evaluating the effectiveness of IVC filters in patients who had DVT/PE, investigators analyzed a database of 3,632 patients who received an IVC filter and 64,333 patients who did not (see Table 3).[13] Among patients with an initial diagnosis of VTE, the results showed no differences between filtered and non-filtered patients in terms of rehospitalization for VTE or PE. However, filtered patients who had an initial diagnosis of PE had a higher rehospitalization rate for recurrent VTE and PE. "This finding not only suggests a non-conferred benefit to using the ICV filter, but also suggests a more adverse outcome in terms of a higher incidence of recurrent clot," stated Wood.

"Having an IVC filter does not mean the patient is immune from having a future clot," he said. A compilation of data from various IVC studies reveals that the risk of developing a PE can be approximately 1% to 2%.[14] "In reality, when you weigh the risks and benefits of using any of the filters available and compare that with anticoagulation therapy, patients are still probably better off being anticoagulated, if possible," according to Wood. "To some extent, the key concern is weighing the risks of bleeding versus thrombotic complications," Wood said.

Regarding the patency of IVC, there are few studies of longitudinal assessment in the literature.[15] One study found a progressive decrease in IVC patency reaching 67% at nine years of follow-up. Patients with PE and anticoagulation failure as a reason for filter placement was a predictive factor of subsequent filter occlusion, compared to other clinical indications with a filter patency of 35% in that group. Complete occlusion was noted in 20% of patients, of whom 50% had leg swelling. "We need to make every effort to remove filters at the earliest juncture," said Wood. The increasing use of retrievable filters is rapidly supplanting the traditional permanent filters and should minimize the incidence of caval occlusion.

In closing, Wood summarized the guideline developed by the British Committee for Standards in Hematology Writing Group.[16] According to the guideline, IVC filters should be used in VTE patients who have a contraindication to anticoagulation therapy. Anticoagulation should be considered in the filtered patient when a temporary contraindication to anticoagulation therapy is no longer present.

Table 2. Cumulative Rate of Clinical Outcomes at Eight Years*

Characteristic	Filter (n=200)	No Filter (n=200)	Hazard Ratio (95% CI)	*P*
Symptomatic pulmonary embolism	9 (6.2)	24 (15.1)	0.37 (0.17–0.79)	0.008
Nonfatal	7	19		
Fatal	2	5		
Symptomatic recurrent deep-vein thrombosis	57 (35.7)	41 (27.5)	1.52 (1.02–2.27)	0.042
Deep-vein thrombosis of the lower limb	55	41		
Thrombosis of filter	26	2†		
Symptomatic venous thromboembolism	58 (36.4)	55 (35.4)	1.12 (0.78–1.62)	0.54
Pulmonary embolism only	1	14		
Deep-vein thrombosis only	49	31		
Pulmonary embolism and deep-vein thrombosis	8	10		
Postthrombotic syndrome	109 (70.3)	107 (69.7)	0.87 (0.66–1.13)	0.30
Edema	92	80		
Varicose veins	48	52		
Trophic disorders	32	39		
Ulcers	5	15		
Death	98 (48.1)	103 (51.0)	0.97 (0.74 -1.28)	0.83
Major bleeding	26 (15.4)	31 (18.5)	0.84 (0.50–1.42)	0.52

*Values are number of patients (cumulative rate in percent) or number of patients.
†Overall, 19 patients among 200 allocated to the no-filter group subsequently received a filter during the study period.

Circulation. 2005;112:416

Table 3. One- and Two-Year Kaplan-Meier Cumulative Incidence of Rehospitalization for Recurrent Thromboembolism

	Outcome, % of Patients			
	Recurrent Venous Thrombosis		Recurrent Pulmonary Embolism	
Group*	Filter	No Filter	Filter	No Filter
No previous thrombolism				
1 Year	8.7†	6.0	3.3†	1.6
2 Year	10.3†	8.1	4.1†	2.2
1 previous thrombolism				
1 Year	11.4†	9.1	4.2†	2.0
2 Year	13.8†	12.3	4.9†	2.7

*No or 1 previous hospitalization in linked record for venous thrombosis or pulmonary embolism.
†*P*<.001, all comparisons of filter and no-filter groups.

Arch Intern Med. 2000;160:2033

New Agents in Anticoagulation

Jack Ansell, MD

Many new small-molecule, direct-factor inhibitors that show promise in medical practice are in development, according to Jack Ansell, MD, from Lenox Hill Hospital in New York, New York. Before presenting the clinical data and characteristics of these new agents, Ansell reviewed the limitations of current anticoagulant therapy.

Traditional anticoagulants include unfractionated heparin, LMWH, warfarin and fondaparinux. "All of these, except fondaparinux, which is specific for factor Xa, are multitargeted; therefore, they affect many clotting factors," said Ansell. Unfractionated heparin has several limitations:

- Protein binding – unpredictable bioavailability due to extensive nonspecific protein binding
- Unpredictability of response – requires monitoring
- Monitoring assays – often inadequate
- Resistance – may develop due to heparin binding to protein
- Potential adverse effects – may cause bleeding, heparin-induced thrombocytopenia and thrombosis

In contrast, LMWH offers the advantages of significantly less protein binding, enabling a predictable dose response, and avoiding both resistance and the need for monitoring. LMWH also has a longer half-life, permitting once- or twice-daily dosing. Furthermore, it is associated with fewer effects on platelets than unfractionated heparin, resulting in a lower incidence of thrombocytopenia. It is associated with increased risk for bleeding in the renally impaired.

Warfarin, the primary anticoagulant used in long-term therapy, is not used commonly in the intensive care setting. This vitamin K antagonist is associated with many limitations; it requires a high degree of monitoring and dose changes.

Turning to the new anticoagulant agents in the pipeline, Ansell noted that almost all are targeted specifically to a particular coagulation factor. Although a look at the coagulation cascade indicates there is an agent in the pipeline targeted to almost any factor, the most advanced in study are targeted to factor X or activated factor X (Xa) and to activated factor IIa (thrombin or IIa).

"The oral factor Xa inhibitors and oral factor IIa inhibitors are particularly suitable for long-term outpatient therapy. If they come to market and prove to be helpful, I think they will also be used on an inpatient basis, including in the ICU," Ansell said.

Debate continues over whether factor Xa or factor IIa is the better target. Ansell noted earlier neutralization of coagulation (i.e., higher up in the coagulation cascade, as in the case of factor Xa) may be better than later neutralization. Another principle asserts that Xa specifically is better because many other important functions of thrombin would be inhibited. Finally, inhibition of factor Xa tends to have a shallower dose response curve, which is desirable. Whether one target is better than the other cannot truly be answered unless head-to-head clinical trials are conducted.

"Fondaparinux (Arixtra; GlaxoSmithKline, Research Triangle Park, NC) was, in a sense, the paradigm initial drug that suggested that Xa inhibition might be better than focused IIa inhibition," he said. Fondaparinux is a chemically synthetic pentasaccharide with pure anti-Xa activity and no antithrombin activity.

Ansell presented data comparing the use of fondaparinux versus LMWH in four clinical trials involving patients who underwent orthopedic surgery for hip replacement, hip fracture or knee replacement.[17] Fondaparinux reduced VTE incidence significantly compared with enoxaparin (Lovenox / Clexane; Sanofi-Aventis, Paris, France); common odds of reduction were 55% ($P<.001$). An increase in bleeding occurred with fondaparinux. "There has been much debate about these studies because the timing of dosing differs for the two agents," Ansell said. "Fondaparinux was dosed much closer to the end of surgery, whereas LMWH was dosed later."

In discussing direct factor IIa (thrombin) inhibitors, Ansell focused on dabigatran etexilate (Pradaxa; Boehringer Ingelheim, Ingelheim am Rhein, Germany). This oral pro-drug binds to the active site of thrombin and neutralizes it, inhibiting both clot-bound and free thrombin. Monitoring is not required with this agent because it has predictable pharmacokinetics and pharmacodynamics. Dabigatran etexilate is not affected by interactions with food. It has a half-life of 12 to 17 hours. Unlike warfarin, it is not metabolized by cytochrome P450 (CYP450) and requires no dose titration. Dabigatran etexilate currently is available in Europe for the treatment of major orthopedic surgery, but it is not available in the United States.

Three major orthopedic phase III trials have compared dabigatran versus LMWH (enoxaparin) in VTE prophylaxis following total knee or hip replacement. In one study, where primary outcome was total VTE and all-cause mortality, dabigatran in doses of 150 mg and 220 mg once daily for 28 to 35 days was non-inferior to enoxaparin 40 mg once daily.[18] Similar results with these doses were observed in a 10-day trial.[19] The third trial, which used the North American dosing of enoxaparin 30 mg twice daily, failed to demonstrate that dabigatran was non-inferior to enoxaparin.[20]

Phase III data are also available for direct Xa inhibitors. Apixaban is an oral, direct, reversible and specific Xa inhibitor that inhibits free and fibrin-bound Xa. "This is important because heparin does not inhibit the activated factor once it binds to fibrin in a clot," Ansell explained. Apixaban exerts no effects on platelet function and does not require monitoring because it has a high degree of predictability. The half-life of apixaban is 10 to 12 hours. It is rapidly absorbed, provides 50% to 80% bioavailability, and is eliminated by both metabolism and renal excretion. Apixaban has minimal drug interactions.

Phase II data yielded favorable results for apixaban in orthopedic surgery. However, a recent phase III trial showed that it did not meet noninferiority criteria compared to enoxaparin in VTE prophylaxis following knee surgery, although the outcomes were very similar.[21] "However, results in total VTE and all-cause mortality were quite similar (8.8% vs 8.99%)," he said. He noted that the incidence of major bleeding was significantly less than with enoxaparin in this trial. A number of other phase III trials of apixaban are ongoing.

"Rivaroxaban, another other Xa inhibitor, also looks promising so far," according to Ansell. This oral, direct reversible inhibitor has many characteristics similar to those of apixaban, although it has a slightly shorter half-life. The U.S. Food and Drug Administration is reviewing its use as a prophylactic agent.

In four orthopedic trials,[22-24] rivaroxaban proved to be superior to enoxaparin, either 40 mg once daily or 30 mg BID. Rivaroxaban also achieved superior results for symptomatic VTE in a recent pooled analysis.[25]

What is the potential impact of these and other new oral anticoagulants? Several possible favorable outcomes may be possible including reduced hospitalizations, reduced burden of management for physicians, and perhaps improved safety, effectiveness and convenience for the patient.

Sponsored by an educational grant from Sanofi Aventis.

Continuing Education Self-Assessment

UPDATES ON THERAPEUTIC OPTIONS FOR DVT AND PE PREVENTION AND MANAGEMENT IN THE ICU

5. What was the incidence rate of post-thrombotic syndrome among patients with DVT, as revealed in eight-year data?
   a. 20%
   b. 35%
   c. 50%
   d. 70%

6. Which of the following is a true statement regarding apixaban?
   a. It is associated with significant bleeding compared with enoxaparin.
   b. It has no effects on platelet function.
   c. It inhibits free, but not fibrin-bound, Xa.
   d. It has been shown to be noninferior to enoxaparin in a phase III trial.