

CONGRESS REVIEW



38th Critical Care Congress Earn CE Credit at www.sccm.org/2009ConRev

Supported by educational grants from Hospira, Baxter, and Sanofi-Aventis

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. For additional information, please call SCCM at +1 847 827-6869 or email education@sccm.org

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).

Faculty Disclosures

Faculty have reported the following disclosures:

Jack Ansell, MD
Lenox Hill Hospital
New York, New York, USA
Consultant, Speakers Bureau
(Sanofi Aventis, Bayer, Bristol-Myers Squibb)

Deborah J. Cook, MD
McMaster University
Hamilton, Ontario, Canada
Study Drug Donation (Pfizer)

E. Wesley Ely, MD, MPH, FCCM
Vanderbilt University
Medical Center
Nashville, Tennessee, USA
Speakers Bureau, Grants, Honoraria
(Lilly, Pfizer, Aspect, Hospira, GlaxoSmithKline)

Jane M. Gervasio, PharmD
Methodist Hospital
Butler University
Indianapolis, Indiana, USA
No Financial Relationships

Daren K. Heyland, MD
Kingston General Hospital
Kingston, Ontario, Canada
No Financial Relationships

Gregory Margolin, DO, FCCM
Internal Medicine, Pulmonary &
Critical Care Associates, LLP
Denver, Colorado, USA
Honoraria (Hospira [manufacturer of Precedex[®]])

Richard R. Riker, MD
Maine Medical Center
Portland, Maine, USA
Research Support (Hospira, AstraZeneca)

Paul Wischmeyer, MD
University of Colorado
Health Sciences Center
Denver, Colorado, USA
Research Support (Products for Clinical Trials);
Consultant (Fresenius Consultant for Abbott, Inc.)

Kenneth E. Wood, DO, FCCM
University of Wisconsin
Hospital & Clinics
Madison, Wisconsin, USA
No Financial Relationships

Find SCCM's policy on resolving conflicts of interest at www.sccm.org/Professional_Development/CE-CME_Information

CE/CME Enduring Material
Release date: June 2009
Expiration date: June 2010
www.sccm.org/2009ConRev

DELIRIUM MANAGEMENT: EVIDENCE FOR CHANGE AND FUTURE DIRECTIONS

Acute brain dysfunction is a new area of focus in critical care. Because coma and delirium in intensive care unit (ICU) patients portend a poor prognosis in both the short and long term, intensivists are called upon to assess patients at the bedside for the presence of delirium and to implement appropriate prevention and treatment protocols.

Identification of Delirium in the ICU: Practical Points and Lessons Learned E. Wesley Ely, MD, MPH, FCCM

“In just the past few years, the number of articles appearing in the literature on delirium in the ICU has skyrocketed,” said E. Wesley Ely, MD, MPH, from Vanderbilt University School of Medicine, in Nashville, Tennessee. “While previously we were doing our best to keep ICU patients alive, we have gotten better at improving survival rates. We now have the luxury of focusing on how well we keep patients alive. Thus, we are paying attention to the main organ that makes us happy in the long term – the brain.”

In hyperactive delirium (the less common form), the patient has potentially terrifying hallucinations; the experience can create symptoms similar to those of post-traumatic stress disorder long after ICU discharge.

However, about 95% of delirium in ICU patients is hypoactive delirium and usually is seen without hallucinations. Instead, patients are quiet and appear undisturbed. “Hypoactive delirium portends a worse prognosis than the hyperactive type,” stated Ely. “Delirium in ICU patients is associated with increased length of stay, increased risk of complications, much higher healthcare costs, and increased mortality rates. We also have data showing a relationship between duration of delirium and acquired dementia in patients after leaving the ICU.”

To be able to make a diagnosis of delirium at the bedside, clinicians should follow a two-step approach to evaluating consciousness:

- Step One: Assess the patient’s state of arousal (i.e., level of consciousness)
- Step Two: Evaluate content (i.e., assess for the presence of delirium)

p-CAM validation tool, a pediatric version of the CAM-ICU, is in development and is expected to be published within the next year.

Features of Delirium

Before discussing the features of delirium, it is important to clarify the terminology used in assessment. If features of delirium are present, the assessment is marked as positive because the patient has failed the test. If the features are absent, the assessment is marked as negative because the patient has passed the test.

Feature One: Alteration/Fluctuation in Mental Status. This assessment is positive if the answer is “yes” to either of the following questions:

- Is this patient’s mental status different from his/her baseline mental status?
- Has the patient had any fluctuation in mental status during the past 24 hours using scales such as the RASS or previous delirium assessments?

Feature Two: Inattention. This is the cardinal feature of delirium. The attention screening examination can employ either an auditory or visual option. The auditory test is used about 90% of the time.

Auditory method: The clinician should instruct the patient to squeeze his/her hand each time the patient hears the letter *A*. The clinician should then spell “S-A-V-E-A-H-A-R-T” or some other string of letters mixing in multiple letter *A*’s (e.g., A-B-R-A-C-A-D-A-B-R-A). Errors of both commission and omission are noted, and if the patient responds correctly to eight of the 10 letters, he or she is able to pay attention (i.e., intact attention, absence of inattention results is negative).

Visual method: If the patient is unable to perform the auditory test or if the resulting score is unclear, clinicians can do visual assessment using 10 pictures as demonstrated on a teaching video accessible at www.icudelirium.org.³

Feature Three: Disorganized Thinking Feature Three is only needed when the patient has Features One and Two of the CAM-ICU but is awake and alert at the time of the examination (i.e., Feature Four is negative). If Feature Four is positive, then technically one does not need to test for Feature Three. To test for disorganized thinking, ask a series of simple “yes” or “no” questions and a command question (asking a patient to hold up a certain number of fingers).

Feature Four: Altered Level of Consciousness. This is actually the clinician’s first assessment; it is made upon entering a patient’s room. The assessment is positive if the sedation score is anything other than alert and calm.

Ely stressed the ease with which delirium can be evaluated in the ICU. “We can diagnose delirium quickly in most patients. If a patient has a fluctuation in sedation scale and is inattentive, he or she is very likely to be delirious. To figure this much out, it only takes about 15 to 20 seconds,” he said. “This is really about improving patient safety and quality of care.”

Confusion Assessment Method for the ICU (CAM-ICU)

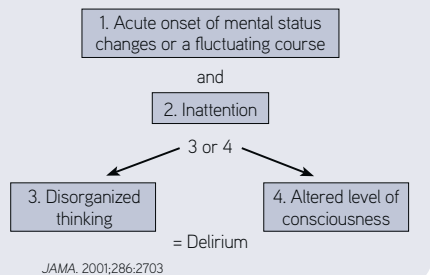


Figure 1. Quick Delirium Tool

Table 1. Intensive Care Delirium Screening Checklist

- Altered level of consciousness
- Inattention
- Disorientation
- Hallucinations
- Psychomotor agitation or retardation
- Inappropriate speech
- Sleep/wake cycle disturbances
- Symptom fluctuation

Clinicians have a variety of well-validated tools available to complete step one. These include the Ramsay Sedation Scale, the Riker Sedation-Agitation Scale (SAS), and the Richmond Agitation Sedation Scale (RASS). Whichever scale is utilized, it should enable the clinician to assess the patient’s level of arousal regardless of current drugs or disease-induced alterations. If the patient does not respond to verbal stimulation, the clinician cannot proceed to step two and assess for delirium.

Two widely used validation tools are used for step two: the Confusion Assessment Methods for the ICU (CAM-ICU) (see Figure 1) and the Intensive Care Delirium Screening Checklist (ICDSC) (see Table 1). The CAM-ICU assesses for the presence or absence of four major features of delirium, as set forth by the American Psychiatric

Association in American Diagnostic Statistical Manual of Mental Disorders.¹ Evaluations using the CAM-ICU typically take 30 to 60 seconds, while assessment via the ICDSC is completed as part of daily nurse charting over 24 hours. A comparison of these two tools reveals that they tend to agree more than 80% of time.² The



Protocols for Prevention and Management of Delirium in Different Patient and ICU Types

Gregory Margolin, DO, CDDP, FCCM

First and foremost, to date there is a paucity of well-validated protocols for the prevention or management of delirium specific to the ICU. However, we can apply best theory and evidence from other situations. Preventing delirium in various acutely ill subpopulations requires a three-pronged approach: optimization of the ICU environment, promotion of slow-wave restorative sleep and reduction of pharmaceutical risk factors.

Gregory Margolin, DO, FCCM, from the University of Colorado, Denver, has applied non-ICU data to the intensive care environment in an effort to optimize the ICU patient experience. Keeping window shades up during the day and turning lights low during the night helps orient patients, promotes melatonin normalcy and preserves circadian processes. Repeatedly talking to patients – even those receiving sedatives – can keep them alert and may preserve cooperative responses. Assurance that the patient is receiving adequate oxygenation and providing frequent access to the patient's eyeglasses or hearing aids may reduce delirium and patient agitation. The data are mixed regarding visits from family members, as they can be either agitating or calming to the patient.

Delirium prevention also is facilitated through promotion of slow-wave restorative sleep. The average patient in the ICU receives only 60 to 100 minutes of slow-wave (restorative) sleep in a 24-hour period; 80% of that is fragmented. "I cannot fathom why we bathe our patients at 2 a.m.," remarked Margolin. Further, he stressed the importance of optimizing patient analgesia before focusing on sedation and urged minimizing patient disruptions between 10 p.m. and 4 a.m.

The third prong in delirium prevention – reduction of pharmaceutical risk factors – is based on leading theories related to the etiology of delirium. Use of dopaminergic agents, anticholinergic agents, and gamma-aminobutyric acid (GABA)-agonists (e.g., benzodiazepine agents and propofol) should be limited. Dopamine excess is strongly linked to the development of hyperactive delirium.⁴ GABA-agonists partially impair slow-wave (restorative) sleep (the exception is their use in alcohol withdrawal to replace alcoholic patients' heightened baseline).⁵ "In paring down the research and looking closely at the major etiologic factors, dopamine excess plus a deficiency of acetylcholine and, of course, disruption of restorative sleep represent the core foundations for an estimated 80% of delirium development."

Currently, there are no Food and Drug Administration (FDA)-approved agents explicitly labeled for the treatment of delirium. A "black box warning" has been assigned to all conventional and most atypical antipsychotic agents (e.g., aripiprazole, clozapine, olanzapine, risperidone, quetiapine, ziprasidone), as an increased mortality rate is associated with these drugs among elderly outpatients with pre-existing dementia (the warning does not apply to dexmedetomidine, which is considered a sedative and not an antipsychotic). "It is important to note that the deaths were largely caused by episodes of heart failure and infections, particularly pneumonias," explained Margolin. "If you're developing an ICU delirium protocol, keep in mind that the black box warning applies to the ambulatory setting and not to highly monitored situations such as the ICU. I'm not saying clinicians can be cavalier about the possibility of aspiration and heart failure. I'm saying that death as an outcome is much lower when the application occurs in a monitored setting."

Management of delirium depends on the subtype of delirium: hyperactive, hypoactive or mixed delirium. The most common type of delirium (mixed or hypoactive) is debatable. One study by Meagher et al indicates that mixed delirium occurs in approximately 46% of delirium cases.⁶ Other reports put mixed delirium rates at 20% to 50% of delirium cases.⁷ Low-activity (or hypoactive) delirium is more prevalent, yet under-recognized. Unfortunately, hypoactive delirium is associated with nearly equal mortality rates. Approximately 60% to 80% of patients with delirium will have hypoactive delirium at some point.⁸ According to the predominant theory, a deficiency in acetylcholine and an excess of serotonin are implicated in the condition's etiology. Use of acetylcholinesterase inhibitors (e.g., rivastigmine, donepezil, physostigmine) possibly can balance the acetylcholine deficiency. Serotonin antagonists (e.g., ondansetron) also may be helpful, particularly in predominantly hypoactive states.

In contrast, hyperactive delirium is the most recognizable but least common subtype of delirium. It is thought to be driven largely

by hyper-stimulation of the central dopamine (D2) receptors. The standard treatment to date has been D2 blockade using agents such as haloperidol or atypical antipsychotics (e.g., risperidone, olanzapine). Though unpublished, one of the most widely adapted methods for treating this subtype is using versions of the "H2A protocol." Developed at Stanford University, it calls for applying a two-to-one ratio of haloperidol and lorazepam administered every six hours to mitigate the effects of delirium.

For all delirium subtypes, the emerging class of alpha-2 agonists (e.g., dexmedetomidine, and – to a lesser extent – clonidine) shows great promise. Theoretically, by reducing central norepinephrine-induced promotion of delirium, promoting restorative sleep, and "dialing down" ascending spinal cord stimuli, one can mitigate delirigenic pathways. Melatonin and the melatonin-agonist ramelteon can aid by inducing (but not maintaining) slow-wave, restorative sleep and sparing patients' cognition, if arousal is desired. Drawing from literature predating 1999, the 2002 American College of Critical Care Medicine's "Clinical Practice Guidelines for the Sustained Use of Sedatives and Analgesics in the Critically Ill Adult" provide a grade C recommendation for haloperidol as the preferred agent in the treatment of delirium in critically ill patients.⁹ The guidelines specify loading with a 2-mg intravenous push, followed by a doubling every 15 minutes until the effect is achieved, thereby establishing a maintenance at 50% of the total loading dose every four to six hours. "When you look at meta-analyses, these doses seem high," remarked Margolin, referring to the application of haloperidol for hypoactive delirium. "I think you're probably going to see adverse effects with these doses – QTc prolongation and extrapyramidal symptoms, such as tardive dyskinesias." These guidelines are being revised. Typically, the dosing of haloperidol in hypoactive delirium is 25% less than hyperactive subtypes. Nearly a decade's worth of additional literature can support an alternative application of atypical antipsychotics, particularly olanzapine and risperidone (the best-studied atypical agents), with equal efficacy and improved safety.

Risperidone and other atypical antipsychotics have been proposed for the treatment of delirium, but no large studies have focused exclusively on the use of atypical antipsychotics in hypoactive delirium. "Anecdotally, the efficacy of risperidone is about 80% in mitigating the symptoms of delirium in the hyperactive, hypoactive and mixed types," Margolin said. Risperidone is the least sedating antipsychotic, making it especially attractive in treating hypoactive delirium. Methylphenidate, which has been studied in palliative care, is showing an emerging role in keeping patients more alert.¹⁰

Margolin summarized suggested protocols for the three delirium types. When treating hyperactive delirium the primary target is a high dopamine level, so haloperidol or another D2 blocker (e.g., risperidone) is the first agent of choice. A baseline electrocardiogram is urged to monitor for potential QTc prolongation. In patients with hypoactive or mixed delirium, atypical antipsychotics (e.g., risperidone) are the best first choice, followed by an acetylcholinesterase inhibitor (e.g., donepezil) and serotonin antagonist (e.g., ondansetron). In all subtypes, promotion of restorative sleep with environmental optimization, alpha-2 agonism and/or melatonin are predicted to become the mainstay of delirium management in the ICU.

As a brief subtext, Margolin took some time to highlight a unique type of delirium, agitated alcohol withdrawal. He stated the best validated protocol is to administer escalating doses of lorazepam or diazepam, commonly referred to as the CIWA protocol. Unfortunately, high doses of benzodiazepines correlate with intubation rates as high as 60% (as a direct consequence of the respiratory depression). Alternative agents to consider include the addition of phenobarbital or baclofen. Margolin endorsed this strategy to lower intubation rates, citing a recent prospective study by Jeffrey Gold, et al¹¹ as well as his own experience in clinical practice. There is insufficient evidence on the use of carbamazepine and gabapentin. Alpha-2 agonists have shown promise in case reports but have not undergone prospective controlled trials. Nitric oxide has been shown to cause harm and should be avoided.

In looking to the future, Margolin urged clinicians to focus on sleep architecture and to watch for more data on promising pharmacotherapies, including alpha-2 agonists and acetylcholinesterase inhibitors.

Alpha-2 Agonists Versus GABA Agonists: Should We Change Standard Practice? Richard R. Riker, MD

“If we’re going to talk about whether we should change our current practice in delirium management among critically ill patients, we need to identify the problems that we should address,” said Richard R. Riker, MD, from Maine Medical Center in Portland.

What Is the Current Practice? What Are the Problems?

The need for adequate early analgesia to mitigate pain cannot be overstated, Riker emphasized. “The painful stimuli to our patients in the ICU are common and frequent.” One study of 6,000 adult ICU patients revealed that patients’ turning and wound dressing changes were more painful than central line placements, femoral catheter removal, and even tracheal suctioning.¹² “Their pain comes from things that happen all day long; things that we often don’t even pay attention to,” Riker said.

Providing an adequate level of analgesia is important. “Neither undersedation nor oversedation is an attractive option,” said Riker. “Both are associated with a long list of adverse effects.”

Riker also noted that, while they are now being revised, the most recent American College of Critical Care Medicine guidelines available were published in 2002.⁹ “These guidelines reflect scholarly work performed through 1999. We’re about nine or 10 years past the evidence that formed the basis of these guidelines,” he noted.

The guidelines support the use of GABA agonists for sedation in critically ill adults. Lorazepam – which produces sedation, anxiolysis, and amnesia – is one of the most common GABA agents used for long-term sedation, yet it has been found to be an independent risk factor for transitioning to delirium among ICU patients.¹³ Other limitations include a slower onset of action than midazolam and an association with propylene glycol toxicity, if moderate or large doses are used. Furthermore, lorazepam can induce retrograde and anterograde amnesia, which may be desirable or undesirable.

Midazolam – another GABA agent with clinical effects similar to those of lorazepam – is recommended for short-term use only. It may accumulate in the setting of renal failure, and it is associated with prolonged recovery after long-term use. When used in combination with opioids, midazolam increases hypotensive effects and is associated with respiratory depression. Like lorazepam, midazolam has been shown to play a role in initiating and prolonging delirium.

Propofol produces several clinical effects, including sedation, hypnosis, anxiolysis and muscle relaxation. Among its adverse effects are respiratory depression, hypotension, decreased myocardial contractility, potential infection, tolerance, elevated serum triglycerides and increased incidence of delirium. This agent also can cause propofol infusion syndrome – a rare, but often deadly, adverse event reported in pediatric and adult patients. Propofol infusion syndrome has even been reported in cases where low doses were administered for short-term use, such as in the operating room. “This is something that we don’t know much about, so we must be vigilant,” Riker said.

What Are the Other Options?

Given the limitations of current pharmacotherapy, Riker suggested that current practice be changed by implementing four strategies:

- Initiating analgesia prior to sedation
- Setting lighter sedation targets whenever possible
- Assessing delirium routinely
- Making better medication choices

“We now have evidence supporting the practice of ‘analgesia-first’ sedation,” said Riker. For example, patients who were randomized to receive remifentanyl before the addition of midazolam for sedation reduced their time on mechanical ventilation by 54 hours and reduced their time to start weaning-extubation by 27 hours, compared with those who received a midazolam regimen first, supplemented by fentanyl or morphine as needed.¹⁴ Furthermore, about 26% of

analgesia-first patients never required or received midazolam, and the rest of the group required a lower midazolam dose compared with the midazolam-first group.

Alpha-2 agonists – clonidine and dexmedetomidine – are becoming the likely first choice medications for sedation-analgesia options for intensive care patients. As sympatholytic agents, alpha-2 agonists limit the further release of norepinephrine. Clonidine is available in Europe as an intravenous agent. It has antihypertensive, analgesic, anxiolytic, and sedative effects and decreases shivering. Common adverse effects include bradycardia, dry mouth and hypotension.

Dexmedetomidine confers similar clinical effects to clonidine, as well as patient rousability and decreased sympathetic activity. Use of dexmedetomidine potentiates the effects of other medications, such as opioids, sedatives and anesthetics. Adverse effects include bradycardia, hypotension, dry mouth, and vasoconstriction with either rapid infusion or very high doses that may lead to hypertension. Nausea has been reported as a rare event.

What Are the Data that Support Change?

Riker referred to data from the Maximizing Efficacy of Targeted Sedation and Reducing Neurological Dysfunction (MENDS) trial, a randomized controlled trial that compared dexmedetomidine to lorazepam in 106 mechanically ventilated ICU patients.¹⁵ The agents were infused for up to 120 hours. The results showed that the lorazepam group tended to be oversedated more commonly than the dexmedetomidine group. Coma occurred significantly less often with dexmedetomidine, and these patients also had more days alive without delirium or coma. A slightly higher incidence of bradycardia occurred in the dexmedetomidine group. “One of the strange findings was that the dexmedetomidine group required higher doses of fentanyl,” noted Riker. “This occurred primarily in patients who had a very deep targeted level of sedation.”

Also presented were findings from the Safety and Efficacy of Dexmedetomidine Compared to Midazolam for Long-Term Sedation in ICU Patients (SEDCOM) study.¹⁶ In this randomized, double-blind multicenter study, 366 patients received either dexmedetomidine or midazolam within 96 hours of intubation and continued treatment until extubation or for up to 30 days. Time to extubation was significantly longer with midazolam than dexmedetomidine (5.6 vs 3.7 days). A significant decrease in the prevalence of delirium was seen in dexmedetomidine-treated versus midazolam-treated patients, regardless of whether delirium was present at baseline or not. A daily arousal assessment was required as part of this study, and time in target sedation was the same in both groups.

“Bradycardia occurred more often in the dexmedetomidine group, but only 4.9% required treatment,” reported Riker. “Surprisingly, a higher incidence of infection developed during the study in the group that received midazolam. This may have been due to direct neutrophil impairment associated with midazolam and other GABA agonists.” When studied, dexmedetomidine did not have that same effect.

Riker emphasized that intensivists should practice the “analgesia-first” strategy, assess patients for delirium routinely, use a lighter level of sedation to avoid oversedation, and consider the advantages that alpha-2 agonists provide.

Sponsored by an educational grant from Hospira, Inc.

Continuing Education Self-Assessment

DELIRIUM MANAGEMENT: EVIDENCE FOR CHANGE AND FUTURE DIRECTIONS

1. Which of the following are pharmaceutical risk factors for developing delirium?
 - a. Anticholinergic agents
 - b. Dopaminergic agents
 - c. GABA agonists
 - d. All of the above
2. Administering remifentanyl before midazolam for sedation had no effect on the amount of time patients were on mechanical ventilation.
 - a. True
 - b. False



INITIATING SAFE PRACTICES: CAN PARENTERAL NUTRITION BE USED SAFELY TO PREVENT CALORIC DEBT AND IMPROVE OUTCOMES?

Can total parental nutrition (TPN) be used safely to prevent caloric debt and improve outcomes? How many calories do critically ill patients really need? Many intensivists today may think their intensive care unit (ICU) is providing adequate nutritional support, but studies – including an international survey that provides benchmarks for performance – suggest that great improvement is needed.

Standardized TPN in the ICU: Safe or Sorry? Jane M. Gervasio, PharmD

In discussing whether standardized parenteral nutrition (SPN) is safe to use in critically ill patients, Jane M. Gervasio, PharmD, from Butler University and Methodist Hospital in Indianapolis, Indiana, examined the rationale for administering SPN to ICU patients and explored its advantages and challenges.

“Parenteral nutrition is a complex drug – and it *is* a drug – and we have to follow the guidelines appropriately,” said Gervasio. In addition to containing lipids, fats, dextrose, multivitamins, and trace elements, TPN provides pharmacologic agents and electrolytes. These can cause complications to both the patient and the compounding procedure.

In fact, TPN is the second most reported drug class associated with medication errors, totaling 22% of all medication reports.¹

The complications of TPN have been associated with morbidity and mortality. They can arise from a full spectrum of problems: inadequate education and knowledge of the prescriber, transcribing errors, compounding errors, mistakes made in the administration, and monitoring errors.

In 2007, The Joint Commission released its National Patient Safety Goals for Hospitals and Critical Access Hospitals, recommending that institutions standardize and limit the number of drug concentrations they use.² The Joint Commission worked with the American Society of Parenteral and Enteral Nutrition (A.S.P.E.N.), realizing that when considering TPN, it is critical to provide patient-specific nutrition, while also looking toward standardization. A.S.P.E.N. stated that SPN goes beyond a premixed bag to also include ordering, labeling, screening patients, and administration. While agreeing on the need to standardize parenteral nutrition, A.S.P.E.N. also recognized that not all patients would benefit from the one-size-fits-all theory. Instead, hospitals should select candidates for SPN.

In discussing how ordering processes can be standardized, Gervasio explained how the forms used at her hospital allow the prescriber to select a standard peripheral formulation, a standard central formulation or a standardized electrolyte profile. Prescribers also may customize a formula. While these standardized formulations are compounded by the hospital's pharmacy, premix solutions are also available. Premix solutions are manufacturer-compounded and are available in various concentrations for both peripheral and central formulations.

The rationale for using SPN is multifold. “SPN improves safety to the patients and reduces costs,” Gervasio said. Safety is improved by minimizing ordering error by the prescriber and misinterpretations of orders by the pharmacist. “The specifics for each solution have already been preloaded into the computer, and the pharmacist simply enters the volume,” she explained. SPN also promotes enhanced patient safety by minimizing calculation and compounding errors, and decreasing contamination risk. Labor costs also are reduced, as less time is required to prepare bags, clarify unclear orders, and correct incomplete or unsafe orders. Standardization reduces inventory, supply needs and waste.

In addition, SPN is designed to meet standard nutrient requirements. While an understanding of the patient's uniqueness is important, identifying which patient's nutritional needs may be met with SPN is advantageous. As an added benefit, standardization provides decision guidance to the prescriber while promoting ease and convenience in the prescribing.

Premix solutions offer several advantages and a few disadvantages. They are sterile, accurate, meet strict quality assurance standards and reduce compounding errors. Contamination risks are decreased, as the bag can be opened only once (when spiked by the nurse). Premix solutions do not need refrigeration, have a two-year shelf life, are readily available, and require less preparation time. However, only the dextrose plus amino acid solution is available in the United States; triple-mix solutions, which contain the fat com-

ponent of TPN, are not available. Fat concentration must be provided via a separate bag. Additionally, if premix solutions are utilized alone, vitamins or minerals must also be added. Errors can occur in administering the solution, as this is a new technology that requires nurses and pharmacists to be properly trained in its implementation.

Is it advisable to use standardized or premix solutions in ICU patients? “Different areas are being investigated to see if we can use these in critically ill patients,” said Gervasio. In some studies, ICU patients receiving enteral nutrition have been given supplemental trophic feeds of SPN. Also being evaluated are dual feedings in ICU patients, in which enteral and parenteral nutrition are started at the same time. The aim of these approaches is to help patients reach nutritional goals earlier.

SPN may be especially advantageous if parenteral nutrition must be initiated over weekends and in the evenings. “The standard formulations are a safety net for our physicians,” remarked Gervasio. “Some of our young practitioners who may not know how to start parenteral nutrition feel more comfortable if they start a liter or 1,500 mL of an SPN. We haven't had a problem when they start with that amount and then get the standard electrolytes going. It provides a starting point from which we can adjust accordingly.”

The limited formula selections can be problematic when managing ICU patients. Standardized formulas have been criticized for failing to meet the high protein needs of critically ill patients. “In reality, with some of the newer triple mixes and high-concentration premixes, as well as with our own standard formulation, we can meet the protein needs of many patients,” Gervasio remarked. “However, the obese population is very challenging because they require a hypocaloric formula and, therefore, less dextrose. It's difficult to meet their protein needs when the amount of dextrose is reduced.”

The greatest challenge in parenteral nutrition is electrolyte management. Parenteral nutrition should be used for maintenance electrolyte management; it should never be used to correct an acute deficiency. Electrolytes have a wide range of normal values, but it is important to identify trends. “For example, even if the patient's potassium values are within the normal range, going from 3.5 to 4 to 4.5 over a three-day period, that's a trend, and it's telling you something,” Gervasio said. “Look for those trends before you make a change.” On the other hand, practitioners should resist reacting to single, nonsignificant abnormal values. Gervasio also advised using electrolytes with intermittent infusions if possible. She noted that electrolytes could be added to premixed solutions, but compatibility issues must be considered.

The use of SPN versus customized parenteral nutrition (CPN) was studied in a 496-bed, tertiary care trauma center with 103 ICU beds in various settings.³ “This was the only study I could find, and it was not robust,” said Gervasio. During 1,298 patient days of parenteral nutrition over a four-month period, 992 patients received SPN and 306 received CPN. More than 3,600 laboratory determinations were made throughout that period. Results showed that laboratory values stayed within the normal range for 73% of patients receiving SPN and 67% of patients receiving CPN. The authors concluded that patients receiving standardized formulations of electrolytes in the parenteral nutrition solutions are more likely to have laboratory serum electrolyte levels within normal levels.

“Where are we headed?” asked Gervasio. “More research is absolutely necessary. An ICU premix formulation may be forthcoming. I would not be surprised to see a variety of premix TPN solutions tailored to different patient populations in the future, similar to what we see now with enteral nutrition.”

Advantages and Disadvantages of Premix Solutions

Advantages

- Provide sterility and accuracy.
- Meet strict quality assurance standards.
- Reduce compounding errors.
- Reduce contamination risks.
- Do not need refrigeration.
- Require less preparation time.
- Offer a two-year shelf life.

Disadvantages

- Premixed TNA (triple mix) solutions are not available in the United States.
- Fat concentration must be provided separately.
- Vitamins or minerals must be added.
- Errors can occur during administration.

Calorie Deficit and Outcome in the ICU: Can We Narrow the Gap? Paul Wischmeyer, MD

"ICU patients are not created equal, so we shouldn't expect the impact or requirements of nutrition therapy to be the same for all patients," said Paul Wischmeyer, MD, from the University of Colorado Health Sciences Center in Denver. "Not only are our patients different, but their illnesses are different – sometimes the disease is hypermetabolic, sometimes it's not. Regardless, muscle wasting is inevitable, and early overfeeding won't fix this. Continued lean body mass loss and calorie deficit have been shown to be lethal. So in some patients, we probably do need to learn how to narrow the gap."

In discussing the metabolism of critical illness, Wischmeyer explained the differences between the stress response and starvation. The stress response leads to increased metabolic rates, increased glucose production, protein catabolism, hyperglycemia, increased catecholamines, increased glucocorticoids and hyperinsulemia. In contrast, starvation leads to decreases in metabolism, calorie use and endocrine function. "Exceeding goal calories during stress reduction will not improve nitrogen balance or decrease catabolic rate as compared with starvation," Wischmeyer said.

During illness, the body must degrade protein to generate the amino acids and other key nutrients to survive. "This protein breakdown is evolutionarily protective," remarked Wischmeyer. He hypothesized that a patient with a larger body mass index (BMI) and increased lean mass would have a better chance for survival because there is more muscle and protein to break down. According to this theory, moderate obesity would be highly protective in heart failure, cancer and other diseases.

Are trauma and sepsis hypermetabolic conditions? Early in their care, patients with trauma and sepsis are not particularly hypermetabolic.

In fact, the more severe their condition, the less hypermetabolic they are. However, as the condition progresses patients become very hypermetabolic. "That's the key time when we cannot fail our patients in their nutritional therapy," he explained.

Patients become hypermetabolic because of the release of tumor necrosis factor (TNF)-alpha and other cytokines during the acute inflammation stage. "Interestingly, when it was first discovered, TNF-alpha was called *cachexin*," Wischmeyer remarked. "It tells the body not to take in much. This raises the question: Why does early, acute inflammation tell us not to eat, and is this relevant to modern medicine? This is what is driving the concept of permissive underfeeding," said Wischmeyer.

In the era of the caveman (prior to ICUs, ambulances, and emergency rooms) hypocaloric feeding made sense because survival in the face of critical illness for more than 24 to 72 hours was not evolutionarily advantageous. Injured organisms were a drain on the primitive community. Thus, early loss of lean mass and the breakdown of amino acids and protein were self-limited.

However, in the modern era of intensive care and emergency medicine, patients are kept alive, and those who are underfed accumulate a caloric debt and continue to lose lean body mass. This is problematic, as research indicates that calorie deficit is lethal. Calorie deficit appears to be highly predictive of mortality, with

a 76% mortality rate reported for ICU patients who developed a 10,000 calorie deficit.⁴

Other studies also have linked poor outcomes with poor caloric balance and insufficient enteral feeding. Gatt and colleagues found that gut failure (defined as enteral/oral tolerance of $\geq 80\%$ of nutritional requirements for ≥ 48 hours at any time during a patient's hospital stay) was more predictive of death than sepsis or renal failure.⁵ In another investigation, which examined caloric debt and complications, Villet observed that caloric deficit was associated with longer ICU stay, more days on mechanical ventilation and more complications.⁶

Most of the data related to the beneficial effects of hypocaloric feeding emanate from permissive underfeeding studies performed several years ago. These investigations evaluated the impact of hypocaloric feeding on short-term outcomes, such as length of stay and infection rates. "However, just because patients leave the ICU doesn't mean they go on to have a good quality of life or even survive two months," said Wischmeyer. "After all, what do we know about our patients after they leave the ICU?"

Research on the continued effect of sepsis on survival indicates that patients treated for sepsis who leave the ICU have a significantly lower survival rate over the next several years compared to a control population.⁷ This finding is true across all age groups, even among younger patients (ages 18 to 44 years).

"One reason for this poor survival rate might be the dramatic loss in lean body mass in our patients," stated Wischmeyer. He related a hypothetical case, in which a major trauma patient becomes septic and develops acute respiratory distress syndrome (ARDS). The patient has a long ICU stay, during which he becomes hypoxic and receives corticosteroids. After he leaves the ICU, he goes into rehabilitation but continues to be weak. He has lost much of his muscle mass and cannot get out of bed. The patient eventually develops a pulmonary embolism and dies.

Survey data has revealed ICUs in the United States do a poor job of delivering adequate calories to patients receiving nutritional therapy, Wischmeyer said. "In comparison with other countries, we also take the longest – on average 60 hours – to start our feeds," he said. "This is likely the major cause of ileus both postoperatively and in the ICU. It is not the surgeon or the disease that cause the ileus. It is the lack of enteral feeding (even for 24 hours) that leads to gastroparesis and gastric intolerance. We must be better at preventing this iatrogenic complication."

Results from the 2007 International Critical Care Nutrition Practice Survey found that patients on average received 1,034 kcal and 47 g of protein.⁸ This resulted in an average caloric deficit of 7,500 kcal and 12,000 kcal over 10 days in lean and obese patients, respectively. In looking at these data, a statistically significant relationship was found between the number of calories delivered and survival in patients with a BMI of <25 or >35 . This relationship indicated that for every additional 1,000 calories fed (up to 2,000 total calories), there was a statistically significant reduction in 60-day mortality in the patient with a BMI of <25 and ≥ 35 . No relationship between calories delivered and mortality was observed in the patients with BMI between 25 and 35. Thus, the decision to aggressively narrow a patient's caloric gap may be very dependent on the patient's admission BMI. We hope to have the opportunity to evaluate this in a future trial, entitled the "TOP-UP" trial.

New Nutrition Support Therapy Guideline Highlights

The Society of Critical Care Medicine and A.S.P.E.N. recently jointly published "Guidelines for the Provision and Assessment of Nutrition Support Therapy in the Adult Critically Ill Patient."¹¹ Highlights include:

- Prior to initiating TPN, early enteral nutrition should be started to prevent ileus.
- Enteral nutrition, supplemented with omega-3 fats, is a clear recommendation for patients with ARDS.
- For burn or trauma patients, consider enteral glutamine and switch to a small bowel tube, if gastric feeding fails.
- Consider parenteral nutrition if a promotility agent and small bowel feeding does not work or if the nutrition goal is not reached after seven days in well-nourished patients (although perhaps it should be started earlier in malnourished patients).

Visit www.learnICU.org to access the complete guideline.

Are We Still Failing to Deliver What Our Patients Need?

Daren K. Heyland, MD

Daren K. Heyland, MD, from Queen's University in Kingston, Ontario, Canada, addressed results of the International Critical Care Nutrition Survey. Conducted in 2001, 2003, 2004, 2007 and 2008, this survey yields important data that help define targets for quality improvement in ICUs. "It enables us to benchmark our performance and see what actually is feasible and reasonable to accomplish," said Heyland.

During its earliest years, the survey collected data from approximately 50 ICUs in Canada. In 2007, the survey extended its reach to include 165 ICUs worldwide, primarily from North America. In 2008, it was expanded further to include Australia, New Zealand and Southeast Asia.⁹

Designed as a prospective, observational cohort study, this international survey seeks to determine current nutrition practice

in the adult ICU setting, illuminate gaps between best practice and current practice, and identify interventions to target for quality improvement initiatives. "It's also designed to enable statistical analyses, so we can identify factors associated with best practice or optimal provision of nutrition," Heyland said.

The 2008 cohort involved 20 consecutive mechanically ventilated patients. Data were collected on hospital and ICU demographics, patient baseline information (e.g., age and admission diagnosis), baseline nutritional assessment and daily nutritional intake for up to 12 days. Researchers followed patients for 60 days, documenting ICU and hospital outcomes.

Participating ICUs were required to have at least eight beds as well as an individual with clinical nutrition knowledge available to collect data. Patients had to be in the ICU for at least 72 hours and mechanically ventilated within 48 hours. A Web-based data capture system was created to enable worldwide participation. A total of 157 ICUs participated in the 2008 survey, with the strongest representation coming from the United States (44 sites). The total number of finalized patients was 2,850. Days of observation averaged 9.4 per patient, providing nearly 24,000 total number of ICU patient days.

More than three-quarters of the participating ICUs resided in teaching or academic hospitals. The average hospital and ICU sizes were approximately 600 and 17 beds, respectively. Patient cases varied; median patient age was 62, and approximately 60% were medical patients. The average Acute Physiology and Chronic Health Evaluation (APACHE) II score was 22, and ARDS was present in 11% of patients within the first 72 hours. The admissions diagnoses spanned a wide range.

"The 60-day patient outcomes data showed that, on average, the patients in this study were on a ventilator for seven days, in the ICU for 10 days, in the hospital for 20 days, and 26% of them died," reported Heyland. "We were dealing with a very sick, ventilated population of ICU patients."

In presenting the nutrition practices results from the 2008 study, Heyland noted that 66% of patients received enteral nutrition, while 9% received parenteral nutrition. These results uphold the recommendation, set forth by the Canadian Clinical Practice Guidelines for Nutrition Support in Mechanically Ventilated, Critically Ill Adult Patients, that enteral nutrition be used over parenteral nutrition.¹⁰ "Wide geographic differences were seen regarding the combined use of enteral nutrition and parenteral nutrition, which averaged 9%," said Heyland.

"For patients prescribed parenteral nutrition, we wanted to know if there was a contraindication to enteral nutrition," Heyland explained. "Survey participants provided a variety of reasons for prescribing parenteral nutrition, although about 50% of them offered no rationale. Others indicated specific contraindications to enteral nutrition, such as small bowel anastomosis, fistula and perforation."

The Canadian clinical practice guidelines also recommend that enteral nutrition be started within 24 to 48 hours of ICU admission. Great variation across geographic regions was documented in the 2008 survey (see Figure 1), with the average site initiating enteral nutrition just before the benchmark of 48 hours. "The value of benchmarking is being able to see how others are performing and what is achievable in other ICUs," remarked Heyland. He noted that in the United States, enteral nutrition typically is started in critically ill patients within the first 50 to 60 hours of admission.

Among suggested strategies to optimize enteral nutrition delivery, the Canadian clinical practice guidelines recommend a feeding protocol that includes consideration of using motility agents and small bowel feeding tubes. According to the 2008 survey, 80% of ICUs have a feeding protocol. Of these, 72% incorporate use of a motility agent and 53% include small bowel feeding. Among all patients involved in the survey, only 16% received motility agents. The most common drug used was metoclopramide. Very few patients in the database (10%) received the combination of erythromycin and metoclopramide. Small bowel feeding is recommended by the Canadian clinical practice guidelines in patients

with gastrointestinal intolerance or risk of aspiration. Overall, use of small bowel feedings was low – instituted by an average 20% of ICUs – and showed wide regional differences. Another strategy to minimize the risks of enteral nutrition delivery – head of bed elevation – was implemented by approximately 30% of ICUs.

The 2008 survey also evaluated the use of intensive insulin therapy in ICUs. The Canadian guidelines recommends that hyperglycemia (blood glucose >180 mg/dL) be avoided in all critically ill patients, and 89% of ICUs said they have a protocol in place to control blood glucose, with most of these protocols targeted between 79.2 to 144 mg/dL.

Finally, the survey assessed the overall performance of ICUs in providing nutrition support. Nutritional adequacy was defined as the number of calories received (from enteral nutrition, appropriate parenteral nutrition, and propofol) divided by the number of calories prescribed. "The results showed that, on average, patients are getting about 50% to 60% of goal calories," reported Heyland. "However, there was one site where patients received 80% of goal calories. If they can do it, why can't the rest of us?" Similar overall performance results were obtained in provision of adequate protein.

Heyland went on to explain the detailed benchmark report sent to survey participants. "Benchmarking lets you identify your strengths and weaknesses as they relate to other ICUs," he said. To create a culture of excellence, the 2008 survey held a "Best of the Best" campaign and recognized 10 ICUs for high nutritional adequacy and adherence to the Canadian guidelines. "Which hospital and ICU characteristics are associated with the best of the best?" asked Heyland. "We found that the presence of a dietitian was by far the strongest predictor of a high ranking," he said. "Being in the United States or China was equally as strong in denoting you as the worst performer," he added.

"Clearly there are opportunities for improvement," Heyland concluded. "We need to close the gap between what we're prescribing and what our patients are getting. Using better feeding protocols will help, particularly those that use motility agents and small bowel feeding. There is also a huge gap in optimizing the use of pharmacutrients." Other areas of improvement include assuring tighter glycemic control and withholding soybean emulsion lipids.

Sponsored by an educational grant from Baxter.

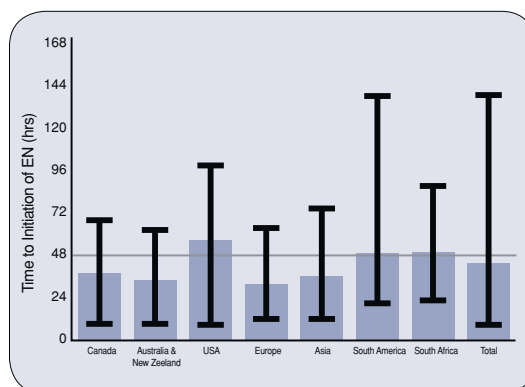


Figure 1. Early vs Delayed Enteral Nutrition (EN).

Continuing Education Self-Assessment

INITIATING SAFE PRACTICES: CAN PARENTERAL NUTRITION BE USED SAFELY TO PREVENT CALORIC DEBT AND IMPROVE OUTCOMES?

- Which of the following statements is true regarding electrolyte management in parenteral nutrition?
 - Electrolytes should not be used with intermittent infusions.
 - Trends in electrolyte levels that appear in the normal range are important to consider.
 - The addition of electrolytes to premix solutions is not recommended.
 - Electrolyte management can be used in parenteral nutrition to correct an acute deficiency.
- Negative calorie balance during a hospital stay is as predictive of mortality as sepsis and renal failure.
 - True
 - False

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.

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

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

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

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.”

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 IVC 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

Group*	Outcome, % of Patients			
	Recurrent Venous Thrombosis		Recurrent Pulmonary Embolism	
	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.