

CONGRESS REVIEW



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

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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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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)

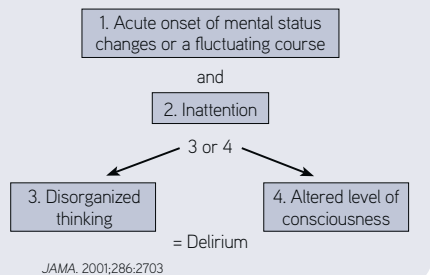


Figure 1. Quick Delirium Tool

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.

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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