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CHEST Recent Advances in Chest Medicine

The Importance of Diagnosing and Managing ICU Delirium*

Brenda T. Pun, RN, MSN; and E. Wesley Ely, MD, MPH, FCCP

ICU delirium represents a form of brain dysfunction that in many cohorts has been diagnosed in 60 to 85% of patients receiving mechanical ventilation. This organ dysfunction is grossly underrecognized because a majority of patients have hypoactive or "quiet" delirium characterized by "negative" symptoms (*eg*, inattention and a flat affect) not alarming the treating team. Hyperactive delirium, formerly called *ICU psychosis*, stands out because of symptoms such as agitation that may cause harm to self or staff, but is actually rare relative to hypoactive delirium and associated with a better prognosis. Delirium is often incorrectly thought to be transient and of little consequence. After adjusting for numerous covariates, delirium is a strong, independent predictor of prolonged length of stay, reintubation, higher mortality, and cost of care. Expanded work on patient safety and recommendations by professional societies have established the importance of delirium monitoring and recommended it as standard practice in ICUs all over the world. This evidence-based review for physicians, nurses, respiratory therapists, and pharmacists will outline why it is imperative that patients be routinely monitored for delirium. This review will discuss modifiable risk factors for delirium, such as metabolic disturbances or potent sedative and analgesic medications. Attention to mitigating risk factors, along with recommended pharmacologic approaches such as antipsychotic medications, may provide resolution of delirium in some patients, while others will persist with refractory brain dysfunction and long-term cognitive impairment following critical illness.

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Key words: aging; analgesia; cognitive impairment; critical care; delirium; encephalopathy; mechanical ventilation; protocols; respiratory failure; sedation

Abbreviations: ASE = Attention Screening Examination; CAM-ICU = Confusion Assessment Method for the ICU; GABA = γ-aminobutyric acid; PAR = Psychological Assessment Resources; RASS = Richmond Agitation-Sedation Scale; SCCM = Society of Critical Care Medicine; VUMC = Vanderbilt University Medical Center; York-VA = Veteran's Affairs TN Valley Healthcare System-York Campus

In an executive summary published by the American Association of Retired Persons and the Harvard Schools of Medicine and Public Health,[1] delirium was considered one of six-leading causes of preventable injury in those > 65 years old. Delirium is an acute confusional state defined by fluctuating mental status, inattention, and either disorganized thinking or an altered level of consciousness. This review will focus on advances in our understanding of delirium in critical care. This update is organized according to key questions that answer the "why, what, and how" of monitoring and managing delirium in critical illness.

Why Should We Monitor for Delirium?

For many years, the critical care community has focused on assessing, preventing, and reversing multiorgan dysfunction syndrome. However, the brain

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has been subjected to relatively little formal study until recently. ICU patients, especially older persons, are among the most vulnerable hospitalized patients for the development of delirium. Studies[2–7] have found that delirium develops in 20 to 50% of lower-severity ICU patients or those not receiving mechanical ventilation, and in 60 to 80% of ICU patients receiving mechanical ventilation. Speaking further to the high prevalence of this organ dysfunction, a study[8] enrolling only nondelirious patients had to exclude 80% of screened ICU patients due to delirium. This problem is neither benign nor self-limiting. ICU delirium is predictive of a threefold-higher reintubation rate and >10 additional days in the hospital.[9–13] Additionally, ICU delirium is associated with higher ICU and in-hospital mortality.[14] Even after controlling for preexisting comorbidities, severity of illness, coma, and the use of sedatives and analgesics, patients with ICU delirium have more than a threefold-increased risk of 6-month mortality compared to those without delirium (Fig 1).[5,9] It is unknown if delirium is the cause of these outcomes or just a marker of an unidentified covariate. However, delirium risks are cumulative; for example, each additional day spent in delirium is associated with a 20% increased risk of prolonged hospitalization and a 10% increased risk of death.[9] It is not surprising that delirium is independently associated with higher ICU costs ($22,346 vs $13,332, respectively) and hospital costs ($41,836 vs $27,106, respectively) compared to those without delirium (Fig 2).[15] Between 10% and 24% of patients experience persistent delirium that may be related to long-term cognitive impairment.[3,16]

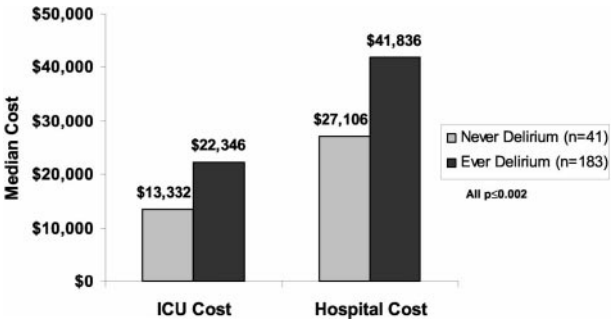

FIGURE 2. The impact of ICU delirium on costs: median ICU and hospital cost per patient. This histogram shows cost according to clinical categorization of "ever delirium" vs "never delirium." Delirium was significantly and independently associated with increased ICU and hospital cost. Used with permission from Milbrandt et al.[15]

While it is well known that patients with preexisting dementia are at risk for delirium (*ie*, "delirium on dementia" [Fig 3]),[4,17,18] data are emerging that indicate delirium may lead to or even accelerate the acquisition of a "dementia-like" entity (*ie*, "dementia following delirium").[19] Approximately one third of ICU patients receiving mechanical ventilation have long-term cognitive impairment that has been doc-

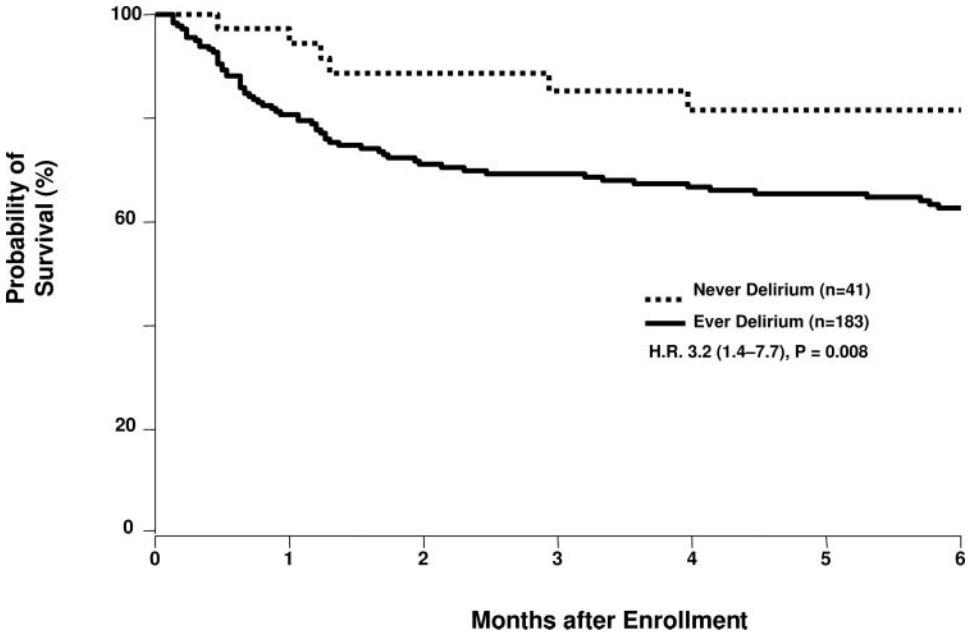

FIGURE 1. Delirium in ICU patients is a risk factor for 6-month mortality. Kaplan-Meier curves of survival to 6 months among ICU patients. Patients with delirium in the ICU had a significantly higher mortality rate than patients without delirium. Used with permission from Ely et al.[9] H.R. = hazard ratio. Data in parenthesis indicate confidence interval.

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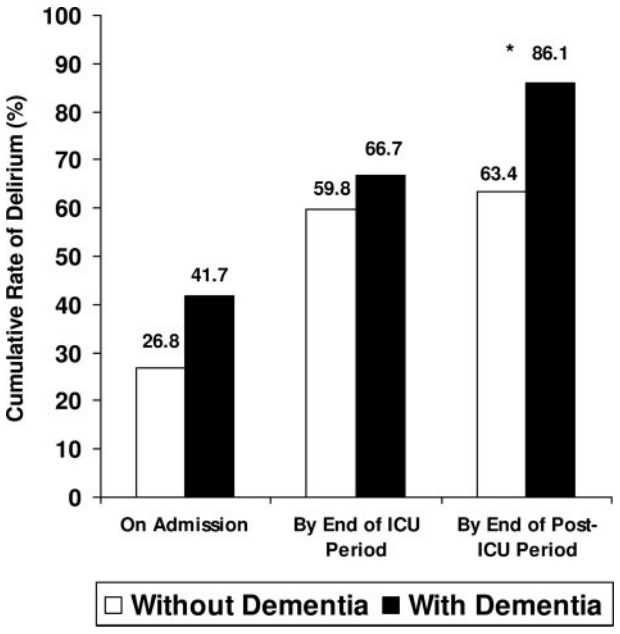

FIGURE 3. Delirium on dementia: cumulative rates of delirium in ICU patients >70 years old with and without preexisting dementia. The graph depicts the cumulative rates of delirium stratified by dementia status in three separate periods: on hospital admission or baseline, by the end of the ICU period, and by the end of the post-ICU period up to 7 days. *Indicates statistical significance with $p < 0.05$ for comparison of groups with and without dementia. Used with permission from McNicoll et al.[4]

umented up to 6 years after hospital discharge.[10,19–24] Several studies[19,25] have found a link between delirium and declining function. Rockwood et al[26] studied cognitively intact geriatric medical patients over 3 years and found that patients with delirium had significantly higher dementia incidence than those without delirium (18.1% vs 5.6%). Dolan et al[27] studied geriatric hip surgery patients and found that patients with delirium were twice as likely to have dementia diagnosed at 2 years. McCusker et al[22] evaluated hospitalized geriatric patients and found that the 1-year mini-mental status examination scores of delirious patients were 5 points lower than patients without delirium. Last, Nelson et al[28] found that the number of days spent in delirium or coma was significantly associated with an increased likelihood of discharge to a post-acute care facility as opposed to home and poorer functional status at 3 months and 6 months. This post-ICU long-term cognitive impairment involves memory, attention, and executive function problems (Fig 4) and leads to inability to return to work, impaired activities of daily living, increased risk of institutionalization, and decreased quality of life.[29–32] The causes of this acquired cognitive impairment are being investigated in two large cohort studies funded by the Veteran's Administration (Measuring the Incidence and Determining Risk Factors for Neuropsychological Dysfunction in ICU Survivors [or MIND ICU] study) and the National Institutes of Health (Bringing to Light the Risk Factors and Incidence of Neuropsychological Dysfunction in ICU Survivors [or BRAIN ICU] study).

Given the poor outcomes associated with delirium, it can no longer be considered a benign problem that will "clear" when the patient is transferred from the ICU. Considering that 9 of 10 seriously ill patients declared they would rather die than survive with severe cognitive impairment,[33] it is imperative that we begin to incorporate brain dysfunction into our prognostication schemes and discharge discussions. This form of organ dysfunction mandates attention and prioritization in the assessment and care of critically ill patients.

What Is Delirium?

Delirium is defined by the *Diagnostic and Statistical Manual of Mental Disorders*[34] as a disturbance of consciousness with inattention accompanied by a change in cognition or perceptual disturbance that develops over a short period (hours to days) and fluctuates over time. Although there are many hypothesized pathophysiologic mechanisms involved in the development of delirium, most are thought related to imbalances in neurotransmitters that modulate cognition, behavior, and mood. Varied terms have been used to describe the spectrum of acute cognitive impairment in critically ill patients, including *ICU psychosis*, *ICU syndrome*, *acute confusional state*, *septic encephalopathy*, and *acute brain failure*.[20,35,36] The current consensus is to consistently use the unifying term *delirium* and subcategorize according to psychomotor symptoms (hyperactive, hypoactive, or mixed).[37] Hyperactive delirium, in the past referred to as *ICU psychosis*, is rare in the pure form and is associated with a better overall prognosis.[38] It is characterized by agitation, restlessness, attempting to remove catheters, and emotional lability.[37,39] Hypoactive delirium, which is very common and often more deleterious for the patient in the long term,[38] remains unrecognized in 66 to 84% of hospitalized patients.[40,41] Amid a busy emergency department ICU shift, hypoactivity on the part of a patient does not seem like a problem and may be missed.[42–44] This subtype is characterized by withdrawal, flat affect, apathy, lethargy, and decreased responsiveness.[38,44,45] In terms of nosology, some refer to the hypoactive delirium as *encephalopathy* and restrict "delirium" to hyperactive patients. However, using separate terms proves difficult since patients may present with a mixed clinical picture or

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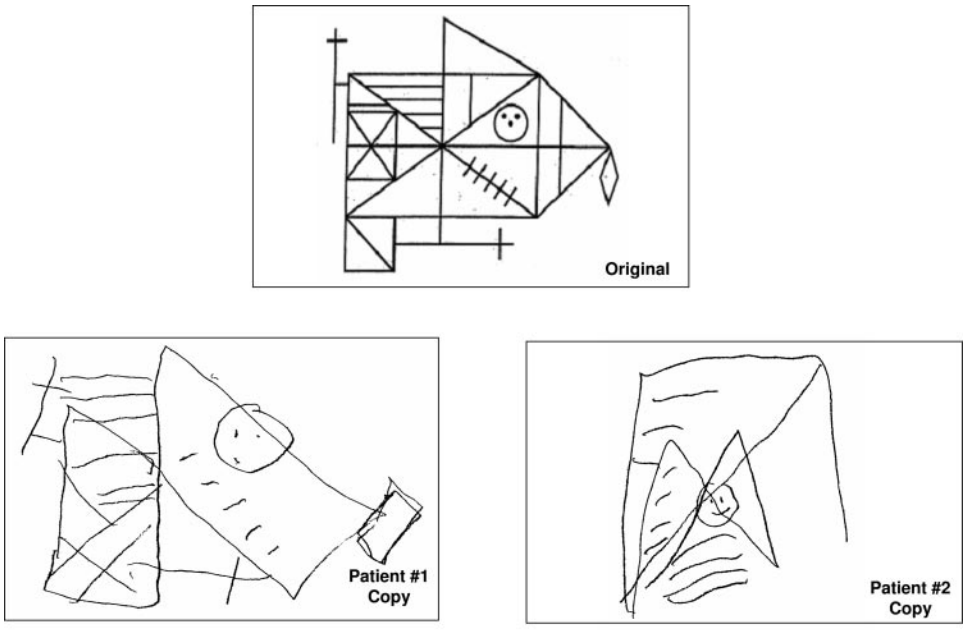

FIGURE 4. Cognitive impairment with the Rey-O Copy complex figure, a test of visuoconstruction in which the patient is asked to copy a complex geometric design while looking at the original. This figure shows the original Rey-O and the examples of two patients tested 3 months after hospital discharge (neither had any detectable baseline cognitive deficits). These images serve as a striking example of neuropsychological deficits that impair the visuospatial and executive abilities of patients long after ICU stay. Reproduced by special permission of the Publisher, Psychological Assessment Resources (PAR), Inc., 16204 North Florida Ave, Lutz, FL 33549, from the Rey Complex Figure Test and Recognition Trial by John E. Meyers, Kelly R. Meyers. Copyright 1989, 1992, 1995 by PAR, Inc. Further reproduction is prohibited without permission of PAR, Inc.

sequentially experience both subtypes. Peterson et al[46] reported the rates of these subtypes in the ICU to be 1.6% hyperactive, 43.5% hypoactive, and 54.1% mixed (Fig 5). Many critical care providers believe hyperactive delirium is more common, but it is merely because these patients attract attention due to their immediate threat to self and others. These data underscore the importance of regular delirium monitoring because many delirium episodes will be invisible otherwise because of negative symptomatology. For "quiet" or hypoactive delirium, it is worth emphasizing that "if you don't look, you won't find."

How Do We Monitor for Delirium?

The Society of Critical Care Medicine (SCCM) guidelines[47] recommend monitoring delirium routinely in patients receiving mechanical ventilation. There are currently two validated tools for monitoring delirium in ICU patients: the Intensive Care Delirium Screening Checklist[48] and the Confusion Assessment Method for the ICU (CAM-ICU).[47] The Intensive Care Delirium Screening Checklist (Table 1) is an eight-item checklist with a sensitivity of 99% and specificity of 64% and interrater reliability of 0.94.[48] Each of the eight items is scored as absent or present (1 or 0, respectively) and summed. A score ≥ 4 indicates delirium. The CAM-ICU was adapted for use in nonverbal ICU patients from the original

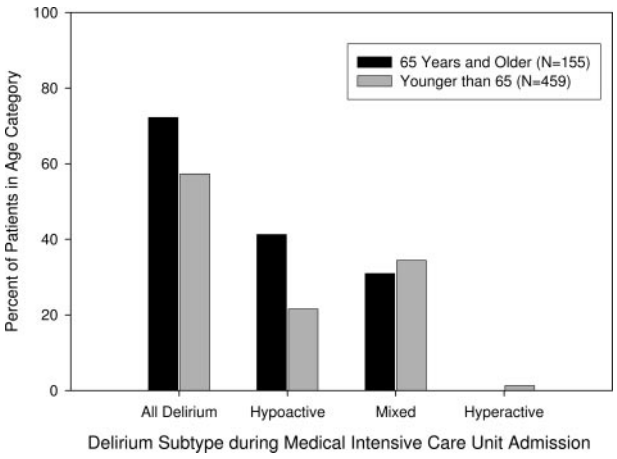

FIGURE 5. Hypoactive and mixed delirium predominate in older and younger ICU patients: percentage of ICU patients with delirium by motoric subtypes (hyperactive, hypoactive, and mixed) stratified by age. Used with permission from Peterson et al.[46]

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Table 1—*ICU Delirium Screening Checklist

Items
Altered level of consciousness (if A or B, do not complete patient evaluation for the period)
A: No response, score: none
B: Response to intense and repeated simulation (loud voice and pain), score: none
C: Response to mild or moderate stimulation, score: 1
D: Normal wakefulness, score: 0
E: Exaggerated response to normal stimulation, score: 1
Inattention (score: 0 to 1)
Disorientation (score: 0 to 1)
Hallucination-delusion-psychosis (score: 0 to 1)
Psychomotor agitation or retardation (score: 0 to 1)
Inappropriate speech or mood (score: 0 to 1)
Sleep/wake cycle disturbance (score: 0 to 1)
Symptom fluctuation (score: 0 to 1)
Total (score: 0 to 8)

*The scale is completed based on information collected from each entire 8-h shift or from the previous 24 h. Adapted from Bergeron et al,[48] with the kind permission of Springer Science and Business Media. Obvious manifestation of an item = 1 point; no manifestation of an item or no assessments possible = 0 point.

Confusion Assessment Method,[49] and includes a four-feature assessment (Fig 6). Sensitivity and specificity values of the CAM-ICU are both > 90%. The CAM-ICU is translated into over a dozen languages, easy to administer, takes on average < 1 min to complete, and requires minimal training.[2,50] CAM-ICU implementation projects within different types of hospitals have reported high compliance and accuracy[51] (Fig 7). A complete description of the CAM-ICU and training materials including videos and translations can be found at www.ICUdelirium.org.

Case Study

The following case study demonstrates delirium assessment using the CAM-ICU. A brief description of CAM-ICU features is needed to guide the reader in these examples. Feature 1 (change in mental status from baseline or fluctuating course) is assessed by comparing current mental status to the patient's prehospital baseline or to the changes in the mental status over the previous 24 h. The patient has feature 1 if his or her mental status is altered compared to prehospital baseline, or is normal but has fluctuated in the past 24 h. Feature 2 (inattention) is assessed using the Attention Screening Examination (ASE). The ASE has two versions: auditory and visual. To conduct the auditory ASE (random letter A), the patient is asked to squeeze the tester's hand when the letter A is said in a series of 10 letters. The visual version is only needed when a patient is unable to physically squeeze (*eg*, the patient is a quadriplegic or has severe critical illness myoneuropathy). For the visual ASE, the patient is shown 5 pictures and then asked to nod yes or no if he/she just saw the original 5 among 10 subsequent pictures. Inattention is deemed to present (*ie*, feature 2 positive) when the patient scores less than eight correct answers on either the auditory or visual ASE tests. Feature 3 (disorganized thinking) is assessed by asking four yes or no questions and having the patient follow a simple command to hold up two fingers with both hands (5 points total). If the patient gets three or fewer correct, he/she has disorganized thinking and is feature 3 positive. Feature 3 is technically only needed for alert and calm patients because they are feature 4 negative. Feature 4 (altered level of consciousness) is measured using a sedation scale such as the Richmond Agitation-Sedation Scale (RASS)[52,53] [Table 2]. If a patient is anything but alert and calm (*eg*, RASS score other than 0), he/she is feature 4 positive. Delirium is present when features 1 and 2 and either 3 or 4 are positive (Fig 6, Table 3).

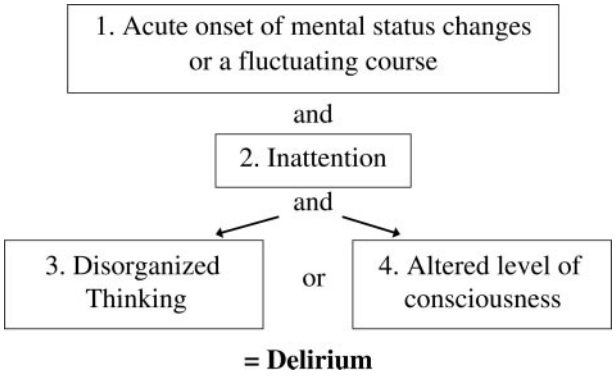

FIGURE 6. CAM-ICU. The diagnosis of delirium requires the presence of acute onset of changes or fluctuations in the course of mental status (feature 1) and inattention (feature 2), plus either disorganized thinking (feature 3) or an altered level of consciousness (feature 4). Used with permission from Ely et al.[3] See www.ICUdelerium.org for step-by-step training materials and a short demonstration video.

Examination 1: Mr. A (day 1) is a 57-year-old patient admitted to the ICU in respiratory distress secondary to pneumonia and was placed on mechanical ventilation. Later that evening, he was found agitated, pulling at his gown, and attempting to get out of bed. At baseline, his family reported that he functioned at a high level and was an engineer. The nurse assessed him to be hyperalert with a RASS of + 3. Attention was assessed by performing the ASE auditory (letter) test; he scored 6 of 10. According to this assessment, features 1, 2, and 4 were positive, and the patient was considered CAM-ICU positive with hyperactive delirium (Table 3). It was not necessary to assess for feature 3 in order to make the overall assessment.

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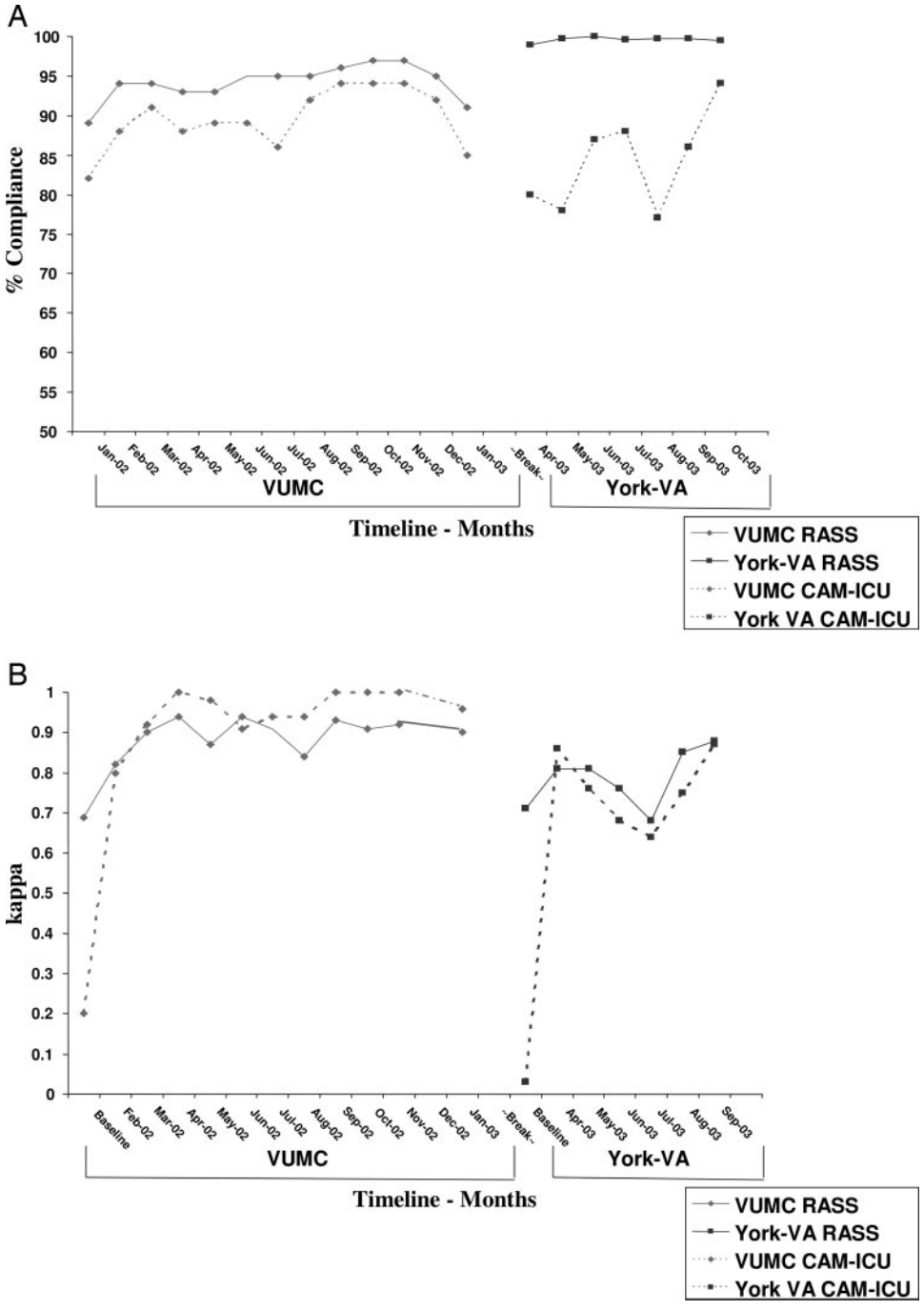

FIGURE 7. Large-scale implementation of sedation and delirium monitoring in the ICU: compliance and agreement within raters. These graphs are from two institutions: a university-based hospital (Vanderbilt University Medical Center [VUMC]) and community-based Veteran's Affairs hospital (Veteran's Affairs TN Valley Healthcare System-York Campus, Nashville, TN). *Top*, *A*: compliance with the two scales over time. *Bottom*, *B*: agreement between bedside medical ICU nurses and expert reference standard raters using the two tools over time. The baseline values noted on the X-axis were obtained during a preimplementation phase to allow comparison with data obtained on subsequent months following educational in-services and hands-on feedback geared to improve the quality of bedside nurses' performance. Used with permission from Pun et al.[51]

Examination 2: Mr. A (same patient, day 2) was administered lorazepam twice during the night. The following day, his nurse assessed him and found that he opened his eyes to a verbal stimulus with sustained eye contact for > 10 s (*ie*, RASS score − 1). He scored only 3 of 10 correct responses on the ASE auditory (letter) test. As on the previous day, features 1, 2, and 4 were positive, yet this time he was in

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Table 2—*The RASS

Scale	Definitions	Description
+4	Combative	Combative, violent, immediate danger to staff
+3	Very agitated	Pulls or removes tubes or catheters; aggressive
+2	Agitated	Frequent nonpurposeful movement, fights ventilator
+1	Restless	Anxious and apprehensive, but movements not aggressive or vigorous
0	Alert and calm	
− 1	Drowsy	Not fully alert but has eye opening to voice and sustained eye contact (> 10 s)
− 2	Light sedation	Briefly awakens to voice with eye opening and eye contact (< 10 s)
− 3	Moderate sedation	Movement or eye opening to voice (but no eye contact)
− 4	Deep sedation	No response to voice, but movement or eye opening to physical stimulation
− 5	Not arousable	No response to voice or physical stimulation

*Adapted from Sessler et al[52] and Ely et al.[53]

hypoactive (quiet) delirium (Table 3). Although not necessary, the nurse assessed for feature 3. The patient answered two of the four simple yes or no questions incorrectly and was unable to follow the "hold up two fingers" command, thus displaying disorganized thinking (feature 3 positive).

Examination 3: Mr. A's (same patient, day 3) breathing improved, and he was successfully extubated. In the previous 24 h, he was assessed with RASS scores − 3 and − 2, but at the current time the patient was sitting calmly in his bed with his eyes open (*ie*, RASS score 0). He scored 10 of 10 on the ASE auditory (letter). This examination revealed that although feature 1 was positive due to fluctuating mental status, features 2 and 4 were not. This patient was no longer delirious (Table 3).

Additional Pearls to Delirium Diagnosis: Someone who is attentive is not delirious. Inattention is pivotal in the diagnosis of delirium. Those meeting some features but not full criteria may have subsyndromal delirium, which is currently being investigated to establish its relationship to intermediate outcomes.

Risk Factors/Etiology: What Are the Modifiable Risk Factors?

One key strategy to prevent or diminish delirium is to identify and modify risk factors that lead to delirium. Inouye et al[54,55] developed a predictive model for delirium in the elderly non-ICU patients that classified risk factors into two categories: predisposing (baseline vulnerability) and precipitating (hospital related or iatrogenic).[55] Numerous risk factors have been identified in non-ICU populations[7,54–57] that fall into these categories, and ICU patients have an average of 11 ± 4 (mean ± SD)[10] of these reported risk factors (Table 4).

Baseline risk factors that predispose patients to the development of delirium include dementia, apolipoprotein E4 phenotype, advanced age, comorbidity, and depression.[4,36,55,56,58] Dubois et al[59] found that preexisting hypertension and smoking (presumably due to relative hypoperfusion and nicotine withdrawal, respectively) were significantly associated with the development of ICU delirium. Similarly, Ouimet et al[14] reported that hypertension and alcoholism were associated with ICU delirium. Pandharipande et al[60] reported in medical ICU patients that increasing age and severity of illness scores were significant independent predictors of transitioning to delirium. Another investigation[4] reported that preexisting dementia was a significant risk factor for delirium. Precipitating and iatrogenic risk factors represent areas of potential modification and thus intervention for delirium prevention and/or treatment. Precipitating factors include hypoxia, metabolic disturbances, electrolyte imbalances, with-

Table 3—*Summary of the Delirium Assessments (See Case Presentation)*

Features	Day 1	Day 2	Day 3
Feature 1: does the patient have an acute change in mental status from baseline or fluctuation?	Positive	Positive	Positive (due to RASS fluctuation)
Feature 2: is the patient inattentive?	Positive	Positive	Negative
Feature 3: does the patient have disorganized thinking?	No need to test	Positive	No need to test
Feature 4: does the patient have an altered level of consciousness?	Positive (agitated, RASS = +3)	Positive (lethargic, RASS = −1)	Negative (awake and alert, RASS = 0)
Overall CAM-ICU: is this patient delirious?	Positive (hyperactive delirium)	Positive (hypoactive delirium)	Negative (not delirious)

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Table 4—*Risk Factors Associated With ICU Delirium*

Preexisting risk factors (baseline vulnerability)
Dementia
Apolipoprotein E4 phenotype
Chronic illness (including hypertension)
Advanced age
Depression
Smoking
Alcoholism
Severity of illness on hospital admission
Precipitating risk factors (hospital related or iatrogenic)
Hypoxia
Metabolic disturbances
Electrolyte imbalances
Sleep deficits*
Congestive heart failure
Sepsis
Prolonged restraint use and immobility
Withdrawal syndromes
Acute infections (systemic and intracranial)
Seizures
Dehydration
Hyperthermia
Head trauma
Vascular disorders
Intracranial space-occupying lesions
Medications
Benzodiazepines
Morphine/fentanyl
Meperdine†
Propofol

*Sleep deficits in ICU patients are hypothesized to cause delirium, although this area is currently in its infancy, and ongoing studies are forthcoming.

†Most consistently associated with non-ICU delirium.

drawal syndromes, acute infection (systemic and intracranial), seizures, dehydration, hyperthermia, head trauma, vascular disorders, immobilization, sleep deficiency, psychiatric medications, and intracranial space-occupying lesions.[36,55,56]

Medications are perhaps the most prevalent modifiable risk factor for ICU delirium. Sedatives and analgesics primarily work by altering neurotransmitter levels throughout the brain, which may be the primary mechanism in delirium development. For example, morphine and "high"-dose benzodiazepines (up to 15 mg) were also linked to delirium in unadjusted analysis.[59] Ouimet et al[14] reported that sedatives and analgesics increased risk of delirium threefold when used to induce coma. Pandharipande et al[60] reported that lorazepam was an independent risk factor for daily transition to delirium (Fig 8), whereas fentanyl, morphine, and propofol trended toward delirium development but were not statistically significant. In a subsequent study[61] of 100 surgical and trauma ICU patients, midazolam (odds ratio, 2.75; $p = 0.002$) and fentanyl (odds ratio, 1.87; $p = 0.05$) exposures were the strongest independent predictors of transitioning to delirium.

Sleep deprivation or loss of circadian rhythm is another potentially modifiable risk factor. Critically ill patients have severe sleep deprivation and disruption of sleep architecture, averaging about 2 h of sleep every 24 h. The causes of sleep deprivation in the ICU consist of excessive noise and lighting, patient care activities, metabolic consequences of critical illness, mechanical ventilation, and sedative and analgesic medications.[62] It is known that disturbance in duration and quality of sleep has detrimental effects on protein synthesis, cellular immunity, and energy expenditure resulting in cardiopulmonary and cognitive effects, yet the relationship between sleep and ICU delirium has not been well characterized.[62,63] Studies are under way to understand how bedside care may be altered to reduce this organ dysfunction and improve immediate and long-term outcomes of ICU patients.

How Should We Approach This Multifaceted Problem?

Nonpharmacologic Prevention and Treatment

In the non-ICU setting, risk factor modification has resulted in a 40% relative reduction in the development of delirium.[64] Modifications include repeated reorientation of patients, repetitive provision of cognitively stimulating activities for the patients, nonpharmacologic sleep protocol, early mobilization, range-of-motion exercises, timely removal of catheters and physical restraints, use of eye glasses and magnifying lenses, hearing aids and earwax

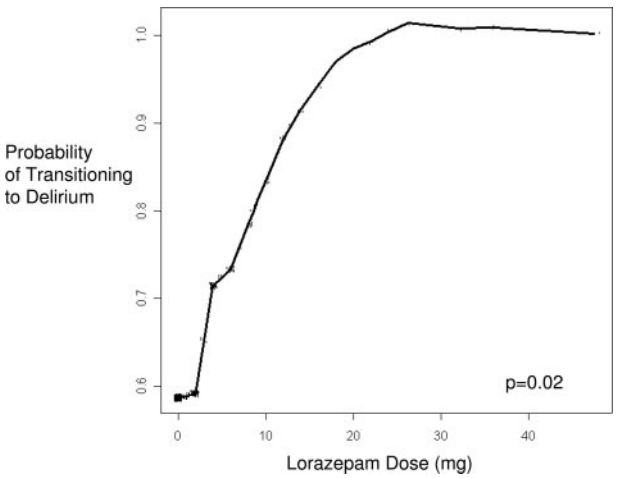

Figure 8. Lorazepam is an independent risk factor for transitioning to delirium in the ICU. The probability of transitioning to delirium increased with the dose of lorazepam administered in the previous 24 h. This incremental risk was large at low doses and plateaued at approximately 20 mg/d. Used with permission from Pandharipande et al.[60]

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disimpaction, adequate hydration, use of scheduled pain protocol, and minimization of unnecessary noise/stimuli. Additionally, delirium-specific multidisciplinary education and nurse-led intervention programs have resulted in a decrease in the duration and severity of delirium.[65,66] However, the success of such strategies will depend on the specific plan, the patient population, and compliance with implementation.[66,67] For example, Lundstrom et al[66] reported that patients on a ward where the staff received specific delirium education and bedside nursing care was reorganized to provide more patient care continuity experienced shorter duration of delirium, shorter hospital stay, and lower mortality.[66] However, Cole et al[67] found no difference in delirium rates in patients observed by an intervention nurse when compared to patients who received standard care. To date, nonpharmacologic "protocolization-of-care" studies have focused on non-ICU populations, but they clearly need to be done in the ICU setting, where the margin for improvement is great due to higher baseline prevalence rates and longer durations of delirium. Currently, investigators are working to determine the most important modifiable risk factors to include in such trials.

Pharmacologic Prevention and Treatment

Coupled with a general lack of awareness of delirium, the absence of level I evidence has resulted in a great deal of indifference regarding ICU delirium and wide variations in pharmacologic treatment.[68,69] Pharmacologic strategies center on either of the following: (1) optimizing the quantity and type of sedative and analgesic medications delivered to patients, or (2) instituting currently recommended medications such as antipsychotics.

Benzodiazepines and propofol work primarily as γ-aminobutyric acid (GABA) agonists, an inhibitory neurotransmitter that affects wakefulness and is thought to be one of the major neurotransmitters involved in delirium etiology. The sedation and amnesia produced by GABA-mimetic drugs result in a decreased level of consciousness but impair slow-wave sleep, which over time may predispose patients to delirium. While these medications have an important role in patient comfort, clinicians must strive to achieve balance in their administration. Daily interruption of sedatives and analgesics and protocolizing their delivery have both been shown to improve patient outcomes.[70–73] The SCCM guidelines[47] recommend that ICU teams set clinically appropriate target sedation levels using well-validated sedation scales and readdress these target levels daily to ensure medication titration to the desired clinical end point.

Novel GABA-receptor–sparing sedative agents may also reduce cognitive dysfunction seen in ICU patients. α_2-Receptor agonists such as dexmedetomidine for short-term sedation in the ICU[74] have stimulated research in this area. Dexmedetomidine inhibits the release of norepinephrine.[74,75] Norepinephrine inhibition and the subsequent downstream affects on neurotransmitters such as histamine, orexin, GABA, and serotonin are similar to that seen in non-rapid eye movement sleep, and are responsible for the sedative property of this drug.[76] Maldonado et al[77] conducted a prospective, unblinded, randomized trial in which cardiac surgery patients sedated intraoperatively at sternal closure were randomized to either dexmedetomidine, propofol, or midazolam. The dexmedetomidine patients had dramatically lower incidence of delirium postoperatively (8%) as compared to those sedated with propofol (50%) or midazolam (50%). These findings should be confirmed in larger trials to determine whether different sedatives (*eg*, benzodiazepines vs dexmedetomidine) are related to a reduced prevalence and duration of delirium, and other important outcomes.

There are currently no drugs with regulatory approval for the treatment of delirium. SCCM guidelines[47,78] recommend haloperidol as the preferred agent for the treatment of delirium based on case series and anecdotal reports. Adverse effects associated with haloperidol include extrapyramidal symptoms, prolongation of the QTc, *torsades de pointes*, neuroleptic malignant syndrome, and akathisia. All patients receiving antipsychotic agents should be monitored for these.[47] Few rigorous stud-

Table 5—*Summary Points on Management of Delirium in the ICU*

Monitor delirium regularly in ICU patients using a valid, reliable tool (*eg*, The Delirium Screening Checklist or the CAM-ICU). Remember that the most is hypoactive and will be missed if not actively "looked for" (Fig 9).
Discuss results of delirium assessments on all patients daily on interdisciplinary rounds.
Identify patients with high number of risk factors for the development or persistence of delirium (*eg*, electrolyte imbalance, fever, addition of new medications; especially those with anticholinergic properties, uncontrolled pain, new onset of congestive heart failure or nosocomial infection, prolonged immobility and restrain use, sleep/wake cycle disturbance).
Review sedation and analgesia therapy, and ensure that the patient is receiving the minimum doses needed to achieve comfort, realizing that narcotics are often used for the double effect of analgesia and sedation. Implement strategies for tight titration (*eg*, nurse-driven, patient-targeted sedation delivery with daily sedation vacations).
Consider the benefit and risk profile of adding medications that might spare the use of sedatives and avoid respiratory suppression (*eg*, haloperidol or atypical antipsychotics).

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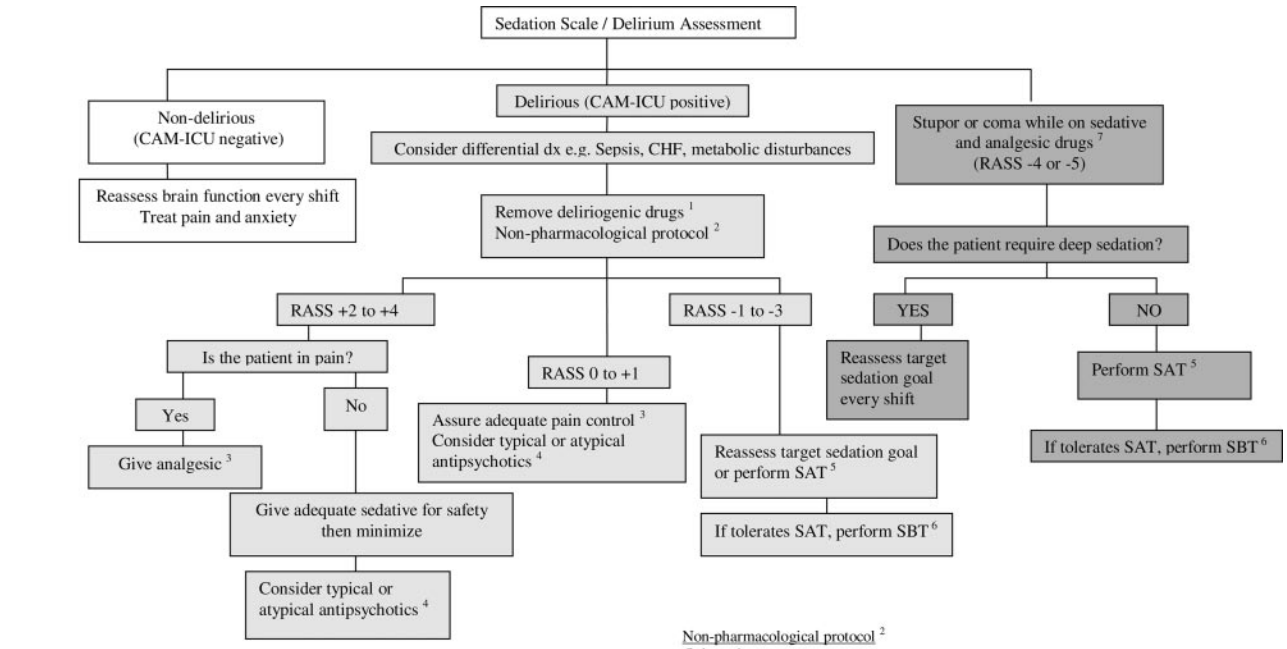

FIGURE 9. Delirium treatment algorithm. This empiric protocol, which is largely based on the current SCCM clinical practice guidelines,[47] is the algorithm the authors use to treat delirium in their ICU. Some aspects are evidence based, while others represent expert opinion and are awaiting refinement through clinical trials. Such protocols need to be updated regularly with new data and also personalized at each medical center according to thought-leaders at that center. Specific recommendations about the choice of antipsychotics to treat delirium have not been described because there are limited data available regarding the preferential use of these medications in ICU patients. The nonpharmacologic interventions recommended in this protocol have shown beneficial results in non-ICU patients; however, extrapolation to the ICU populations is speculative at this time. H2 = histamine type 2; max = maximum; dx = diagnosis; CHF = congestive heart failure; CPAP = continuous positive airway pressure; PEEP = positive end-expiratory pressure; Sats = oxygen saturation. This figure is available as a full landscape PDF file at http://icudelirium.org/delirium/training-pages/DeliriumProto%2001_30_07.pdf.

ies have been done to evaluate the efficacy of haloperidol or other antipsychotics in delirious patients.[79] One report[80] found that prophylactic treatment with low-dose haloperidol in elderly hip surgery patients reduced the duration and severity of delirium but not its incidence. A retrospective study[81] found that patients who received haloperidol within 2 days of initiation of mechanical ventilation had a significantly lower hospital mortality rate when compared to patients who did not receive haloperidol.

The atypical antipsychotics (*eg*, aripiprazole, olanzapine, quetiapine, and ziprasidone) may also be helpful in treating delirium. Their mechanisms of action are similar to haloperidol, but in addition to dopamine they affect a variety of neurotransmitters, including norepinephrine, serotonin, histamine, and acetylcholine.[79,82–84] Skrobik et al[83] reported that olanzapine and haloperidol had similar affects on delirium in medical and surgical ICU patients, but that olanzapine was associated with fewer adverse events. The results of this initial study[83] should be confirmed in placebo-controlled trials. Kato et al[85] reported a case study suggesting that genotyping may impact the treatment effect of antipsychotic drugs. A patient with a CYP2D6 poor metabolizer genotype had persistent delirium and severe extrapyramidal symptoms when treated with risperidone, which is

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metabolized by CYP2D6. The patient was switched to quetiapine (metabolized by CYP3A4), and the delirium cleared within 2 days without side effects. Considering individual-patient metabolic enzyme profiles may be a tool in guiding safer and more efficacious pharmacotherapy, but this is a controversial topic that is in its infancy.

In early 2005, the Food and Drug Administration issued an alert[86] that atypical antipsychotic medications are associated with mortality risk among elderly patients. This warning was supported by a large metaanalysis of demented outpatients who received antipsychotic medications for treatment of psychotic symptoms.[87,88] Subsequently, Wang et al[89] reported that haloperidol had an even higher mortality risk in non-ICU elderly patients than atypical antipsychotics. No placebo-controlled trials involving haloperidol and/or atypical antipsychotics have been done in the ICU. Milbrandt et al[81] reported on a retrospective chart review in which haloperidol use in the ICU was associated with improved survival. The data above emphasize the need for more research in this area and underscore the importance of exercising caution when treating delirium.

Conclusions

Although delirium research in critical care is rapidly maturing, the weight of evidence already demonstrates that critical care clinicians cannot afford to ignore this form of organ dysfunction in our patients (Table 5). If we are to be comprehensive in our approach to monitoring and managing organ dysfunction, the brain should be a very active component of our daily discussion at the bedside in the ICU. This article has outlined key reasons to "tip" delirium onto the physician's "radar screen" and has supported each reason with evidence. Where evidence is emerging or not yet existent, we have also acknowledged this and offered timely solutions for the clinician.

How might the physician begin this process of change in practice? First, one can start by making it clear that as a climate of patient safety is instilled in the institution, delirium will be a priority. Second, as recommended by the clinical practice guidelines, implement goal-directed sedation and delirium monitoring, frequent charting, and discussion on rounds as part of a daily ICU routine. Third, the physician should discuss preventive strategies that make sense for patients in the ICU setting. In addition to the specific recommendations for the management of pain, sedation, and delirium, the 2002 SCCM guidelines[47] include a treatment algorithm. Additionally, we have included a sample delirium treatment algorithm (Fig 9). This article has reviewed several non-ICU randomized trials with positive findings that, coupled with obvious issues such as correction of metabolic disturbances, avoiding overuse of psychoactive medications and prolonged restraints, and attempts at improving sleep, may offer an initial protocolized approach while awaiting results of ICU-specific investigations. As pointed out by Polderman and Smit,[90] "Inattention may be a basic feature of delirium, but it should not be a component of our attitude toward delirium in the ICU."

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