ICU delirium: an update

Shirley F. Jones[a] *and Margaret A. Pisani*[b]

Purpose of review
Delirium is frequently encountered in the ICU and is associated with significant adverse outcomes. The increasingly recognized consequences of ICU delirium should enhance efforts to improve recognition and management of this serious problem. We aim to review the recent literature on ICU delirium, including risk factors, detection, management and long-term impact of disease.

Recent findings
We present the most recent evidence on risk factors for ICU delirium and its persistence. In addition, we aim to clarify some of the confusion surrounding the tools for detection and their limitation in practice. The literature reflects long-term neurocognitive impairments following ICU delirium and supports efforts to reduce these negative outcomes using protocol-driven sedation and ventilator management. Although haloperidol is widely accepted as the preferred pharmacologic treatment for delirium, its use is not seeded in robust evidence. Limited studies reflect the safety of atypical antipsychotics for treatment but lack clear improvement in delirium-related outcomes. We place an emphasis on the use of protocols to reduce the use of sedatives, particularly benzodiazepines in the management of ICU delirium.

Summary
Delirium remains an underrecognized and underdiagnosed problem. Detection tools are readily available and easy to use. Further understanding of risk factors is needed to identify most susceptible individuals and plan management, which should include prevention and therapy based on available evidence.

Keywords
delirium, diagnosis, ICU, outcome, risk factors, treatment

INTRODUCTION

ICU delirium is a common consequence of critical illness. In nonventilated ICU patients, nearly 50% of patients develop delirium [1], whereas the incidence approximates 80% [2–4] in intubated patients. Despite the cause of critical illness, rates of delirium are high.

The clinical practice guidelines of the Society of Critical Care Medicine support the routine assessment for delirium in ICU patients [5]. However, surveys of intensivists reveal that standardized detection tools and prevention strategies are not being utilized though readily available [6]. There is a strong relationship between the development of ICU delirium and negative outcomes making detection and early treatment imperative. ICU delirium is associated with prolonged mechanical ventilation [7], longer hospital and ICU lengths of stay [8], and a high rate of after discharge institutionalization [9]. Although factors to identify those at risk are important, the burdening health-related costs [10] serve as an impetus to develop and implement strategies for detection, treatment, and prevention. The long-term negative outcomes lend strength that the impact of delirium extends beyond recovery from the primary illness that necessitated ICU admission. This article will serve to review the most recent evidence on the risk factors, detection, outcomes, and management of ICU delirium.

RISK FACTORS

Identification of risk factors for ICU delirium is paramount in detecting and designing of prevention and treatment strategies and in identifying means of reducing cost utilization. Previous studies have identified age above 65 years [11], cognitive

[a]Scott and White Healthcare/Texas A&M Health Science Center, Temple, Texas and [b]Yale University School of Medicine, New Haven, Connecticut, USA

Correspondence to Shirley F. Jones, MD, FCCP, Assistant Professor of Medicine, Scott and White Healthcare/Texas A&M Health Science Center, 2401 South 31st Street, Temple, TX 76508, USA. Tel: +1 254 724 9887; e-mail: shjones@swmail.sw.org

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KEY POINTS

- Valid screening tools and their appropriate use are necessary to accurately diagnose ICU delirium during routine ICU practice.
- Long-term cognitive impairment is related to duration of ICU delirium.
- Protocolized management of the mechanically ventilated patient aimed to reduce sedation results in significantly improved clinical outcomes, including risk reduction of cognitive impairment.
- The use of antipsychotics for the management of ICU delirium lacks significant evidence.
- A detailed understanding of the relationship between patient and disease-related risk factors for ICU delirium and its persistence is needed to risk stratify and improve healthcare utilization.

impairment [12,13], severity of illness, alcoholism [14], hypertension [14,15], elevated creatinine [13], and medications such as benzodiazepines as risk factors for delirium [11]. Disease-related factors serve as a focus of continued research.

Guillamondegui *et al.* [16▪] examined hypoxia as a risk factor for ICU delirium and long-term cognitive impairment in patients admitted with multiple injuries, but no evidence of intracranial hemorrhage, to a trauma ICU at a large academic center. Hypoxia was defined as either oxygen saturation less than or equal to 90 or less than or equal to 85% for more than 5 min during the initial 48 h of admission and was present in 74 and 36% of the population, respectively. Fifty-seven percent of the sample tested positive for delirium. Fifty-five percent of the participants evaluated 12 months after hospital discharge had evidence of cognitive impairment. Univariate and multivariate analysis of data did not reveal any significant association between hypoxia and ICU delirium or cognitive impairment. It is important to emphasize that the sample population had 'mild' forms of traumatic brain injury of which over half developed delirium and many experiencing long-term cognitive impairment.

Patients with persistent delirium may require prolonged length of ICU stay for monitoring despite resolution of the illness triggering ICU admission, that is, septic shock. The higher cost utilization may be due to the greater need for nursing care due to reluctance to transfer delirious patients, thus prolonging ICU length of stay. Recognizing factors for persistent delirium is needed to identify those at highest risk and plan cost-saving strategies.

Pisani *et al.* [17▪▪] prospectively examined a cohort of 309 consecutive older (age $\geq$60 years) medical ICU patients to identify baseline patient and ICU-related risk factors for persistent delirium after ICU discharge. Persistent delirium was defined as delirium occurring in the ICU and continuing upon discharge to the ward. Of the 173 patients with ICU delirium who survived and were transferred, 58% had persistent delirium. Associate factors included age 75 years or more [odds ratio (OR) 2.52, 95% confidence interval (CI) 1.23–5.16], opioid (morphine equivalent) dose more than 54 mg per day (OR 2.90, 95% CI 1.15–7.28), and haloperidol (OR 2.62, 95% CI 0.95–7.35). Dementia and change in code status to do-not-resuscitate were notably less robust in association, but trended toward significance [17▪▪]. The authors finding of haloperidol use as a risk factor for persistent delirium is worthy of additional attention. Although this finding could simply represent differences in delirium management practices among intensivists caring for an older population, the relative paucity of evidence on the use of haloperidol for the treatment of delirium draws the conclusion that research, particularly randomized controlled trials of haloperidol in delirium, is needed. Furthermore, the finding of opioid use as a risk factor for persistent delirium contrasts to previous literature [11,13] and overall reflects a mixed effect of this drug class on delirium [15]. Due to the higher risk of 1-year mortality associated with persistent delirium [18], further research is needed.

DETECTION

Despite the data that only 25–59% of intensivists routinely screen for delirium [6,19▪], its high prevalence and associated negative outcomes emphasize the importance of detection. According to a recent survey, 62% of intensivists in North America rely on general clinical assessment to screen for delirium. It is well recognized that bedside general assessment by physicians lacks sensitivity to detect delirium [20–22]. Similarly, observations by ICU nurses under close 1 : 1 or 1 : 2 nurse patient ratios are also insufficient. In a study of ICU nurses at a single center, 35 matched assessments of delirium were made using observations by the bedside ICU nurse and with the Confusion Assessment Method for the ICU (CAM-ICU) performed by a trained nurse evaluator. Agreement between the two methods was poor ($\kappa = 0.22$). The sensitivity of bedside assessment was only 27% [23▪]. Hence, validated delirium assessment tools are necessary for proper diagnosis.

A variety of tools exist for the detection of delirium, but only the CAM-ICU, Intensive Care

Delirium Screening Checklist, Delirium Detection Score (DDS), Cognitive Test for Delirium, and the Neelon and Champagne Confusion Scale have been validated in the critically ill [21]. The variety of delirium detection tools available has led to confusion as to which tool to use. Luetz *et al.* [24▪▪] compared validity and reliability of the CAM-ICU, Nursing Delirium Screening Scale (Nu-DESC), and DDS for detection and assessment of delirium in surgical ICU patients at a single university hospital. Evaluations were made by trained staff members and compared with the reference standard by a delirium expert using the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV). The CAM-ICU and Nu-DESC had high sensitivities (CAM-ICU 81% and Nu-DESC 83%), whereas the DDS's was poor at 30%. Both the CAM-ICU and DDS had high specificity (CAM-ICU 96% and DDS 91%), whereas the specificity of Nu-DESC was 81%. Interrater reliability for CAM-ICU, DDS, and Nu-DESC was 0.89, 0.79, and 0.68, respectively. Due to the poor sensitivity of the DDS, it should not be used as a screening tool.

In 2001, Ely *et al.* [2] published validity and reliability studies of the CAM-ICU performed by two study nurses showing high sensitivities (93–100%), specificities (98–100%), and interrater reliability ($\kappa = 0.96$; 95% CI 0.92–0.99) compared with assessments by delirium experts using the DSM-IV. However, van Eijk *et al.* [25▪▪] tested characteristics of the CAM-ICU when conducted by ICU nurses on a routine basis. A prospective multicenter study of 10 ICUs in both academic and non-academic centers in the Netherlands reported significant degrees of disagreement, reduced sensitivity, and specificity of the CAM-ICU when used in routine practice. Using the gold standard assessment made by delirium experts using the DSM-IV, 282 participants were classified as either awake and not delirious, delirious, or comatose. The experts classified 38% of patients as awake and not delirious, 28% as delirious, and 34% as comatose. In contrast, ICU nurses performing routine care underdiagnosed delirium (56% were CAM-ICU negative) and comatose patients (28%). The CAM-ICU in routine practice, conducted by ICU nurses, demonstrated a sensitivity of 47% (95% CI 35–58), specificity of 98% (95% CI 93–100), positive predictive value of 95% (95% CI 80–99), and negative predictive value of 72% (95% CI 64–79). Interrater reliability was $\kappa = 0.63$. Interestingly, all facilities used lectures and written information for training of the CAM-ICU, and most centers provided individual bedside training and frequent performance of CAM-ICU daily. Centers reporting that the results of the CAM-ICU were always used by the physicians had higher sensitivities, implying that accuracy of detection is dependent upon management or buy-in of physicians. This article suggests that as many as half of patients are undiagnosed in routine practice despite use of the CAM-ICU. Measures to enhance education on ICU delirium across the healthcare spectrum and to ensure reliability among evaluators is needed.

Although prediction models and screening tools currently serve as the foundation for delirium detection, research examining serum biomarkers may prove useful in the future. In a small case–control study of 30 individuals with delirium, concentrations of brain-derived neurotrophic factor (BDNF) and neuron-specific enolase (NSE) were higher on ICU admission in patients with delirium compared with those without delirium [26▪]. BDNF and NSE are proteins specific to neurons and glial cells, and higher levels are associated with cell death [27]. Interestingly, there was no correlation with higher levels of either protein 1 day prior to a positive screening test for delirium. On the basis of this study, serum testing for BDNF or NSE is not ready for routine use, but does warrant further investigation.

OUTCOMES

The association between ICU delirium and negative outcomes has been well recognized. ICU delirium is associated with prolonged hospital length of stay [2,4,8] post-discharge institutionalization [9] more days requiring mechanical ventilation [7] an increased risk of death [4] and higher costs [10]. Recently an increasing amount of literature on neuropsychological and cognitive outcomes of delirium in noncardiac surgery patients has emerged. Although cognitive impairment in survivors of critical illness has been recognized [28–30], new is its relationship to the duration of delirium. In a prospective cohort study of mechanically ventilated patients at a single academic center, 76 survivors of critical illness underwent a battery of neuropsychological testing at 3–12 months after discharge. At 3 months, 50 patients (79%) had evidence of at least mild/moderate cognitive impairment. Fifty-two patients completed the 12-month assessment, and 37 (71%) still had findings of cognitive impairment. The duration of ICU delirium was an independent predictor of cognitive impairment 3 months after enrollment. An increase from 1 day of delirium to 5 days was independently associated with a one-half standard deviation decline in the cognitive battery mean score. This effect was independent of the number of mechanical ventilator days [31▪▪]. This study serves as an impetus to design

and implement future trials aimed to reduce the neurocognitive consequences of ICU delirium.

The neuropathologic impact in patients diagnosed with delirium was evaluated in a retrospective study of brain autopsies in patients who had ICU delirium and subsequently died. Six of seven patients had lesions attributable to hypoxia or ischemia. Severe sepsis was the most common cause of death (six of seven). The hippocampus was the most common site of injury in five of seven patients [32]. Additional studies comparing postmortem findings between patients with and without delirium are needed.

MANAGEMENT

Strategies for management of delirium aim at reduction of contributing factors, treatment of comorbid disease, and pharmacologic management. Despite the support of the Society of Critical Care Medicine on the use of haloperidol for pharmacologic treatment of delirium [5], this practice lacks evidence. In a single retrospective study, use of haloperidol was associated with reduced in-hospital mortality [33]; however, extrapolation to improvements in outcomes associated with delirium should not be made, as delirium was not measured.

Due to potential side effects of haloperidol that include torsades de pointes, prolongation of the QT interval and extrapyramidal effects, clinicians may prescribe atypical antipsychotics. Unfortunately only three studies conducted exclusively in an ICU population exist that examined atypical antipsychotics for delirium. In the Modifying the Incidence of Delirium trial, delirium free or coma free days were not different between subjects receiving olanzapine, haloperidol or placebo [34▪▪]. In a prospective, multicenter, double blind randomized placebo-controlled trial, quetiapine was associated with shorter time to first resolution of delirium and shorter duration of delirium compared with placebo with no significant differences in length of stay or days with mechanical ventilation [35▪▪]. However, the study did not reach targeted enrollment. A posthoc analysis showed a shorter duration of individual symptoms of delirium: inattention, disorientation, and symptom fluctuation with use of quetiapine [36▪]. Risk of negative long-term outcomes with individual symptoms is unknown. Skrobik *et al.* [37] conducted a prospective randomized controlled trial on the safety and efficacy of olanzapine versus haloperidol. Severity of delirium improved, as well as a reduction in the need of sedatives in both arms without significant differences. However, patients receiving haloperidol had more extrapyramidal effects. Devlin and Skrobik [38▪▪] reviewed the literature on use of antipsychotics for ICU delirium. There is a lack of evidence for its use in prevention. Future research will include studies of blonanserin, a novel atypical antipsychotic with potent dopamine D(2) and serotonin 5-HT(2) antagonist properties. The literature on its use in ICU delirium is limited to a single retrospective study showing reduction in delirium scores [39]. A great need exists for future studies examining the role of antipsychotics for treatment and prevention of delirium [38▪▪].

Equally emphasized in the management of ICU delirium is the importance of elimination of iatrogenic causes including the common practice of judicious use of sedation and analgesia for relief of pain and discomfort. Sedation, particularly benzodiazepines are identified as risk factors for the development of delirium. Protocolized strategies to reduce sedation and analgesia use in the ICU should be implemented. Skrobik *et al.* [40▪] examined clinical outcomes of a preeducational and posteducational initiative and protocol for ICU staff to recognize pain, agitation and delirium. The hypothesis was that management of sedation and pain based on target-controlled and protocol-driven pharmacologic and nonpharmacologic management would result in improved outcomes and reductions in delirium. Posteducational outcomes included reductions in amounts of benzodiazepines used, rates of iatrogenic coma, length of stay, and days with mechanical ventilation. Though rates of delirium were unchanged; rates of subsyndromal delirium were reduced. In the Awakening and Breathing Controlled Trial, paired daily interruption of sedation (SAT) and followed by a spontaneous breathing trial (SBT) was associated with reductions in benzodiazepine use by half compared to the control group. Use of this protocol resulted in more ventilator free days, shorter time to discharge from the ICU and from the hospital, less days spent in coma, and 1-year mortality [41]. Clearly, use of protocol driven management aimed to reduce sedation has more benefits than the effects on delirium alone.

With an emphasis on reducing sedation, questions arise to the possible psychological consequences of this shift in paradigm. Cognitive impairment is less common in individuals receiving decreased sedation with similar degrees of depression and posttraumatic stress disorder compared with patients receiving more sedation. In this substudy of data from the Awakening and Breathing Controlled Trial, cognitive, psychological and functional/quality of life measures performed at 3–12 months after discharge, showed that cognitive impairment was less common in patients who

received a paired SAT followed by a SBT protocol. An absolute risk reduction of cognitive impairment of 20% was observed in the intervention [42▪▪]. The results of this study underscore the negative consequences associated with benzodiazepine use beyond its effects on ICU delirium.

Furthermore, a coordinated ABCDE approach may be a useful strategy for management of the mechanically ventilated patient [43▪,44▪]. The ABCDE approach bundles Awake and Breathing coordination for liberation from sedation and mechanical ventilation, attention to Choice of sedation, Delirium monitoring, and Early mobility and exercise. More novel sedation practices include the use of dexmedetomidine. In the Maximizing Efficacy of Targeted Sedation and Reducing Neurological Dysfunction trial, patients receiving dexmedetomidine spent more days alive without delirium and coma compared with lorazepam [45]. In the Safety and Efficacy of Dexmedetomidine Compared with Midazolam trial, there was less delirium in patients randomized to receive dexmedetomidine compared with midazolam [46]. The positive effects of early mobility and exercise are highlighted in two randomized controlled studies. ICU patients who receive early mobility spend 6 days less in bed and had shorter ICU and hospital lengths of stay after adjustment for confounders [47]. When paired with sedation interruption, 59% of patients receiving early exercise and mobilization were able to return to independent functional status compared with 35% ($P = 0.02$) in the control group with fewer days with delirium [48].

CONCLUSION

Delirium is a serious complication of critical illness. The notion that delirium is an unalterable outcome is unacceptable. Further research is needed to understand risk factors, design best practices, and to educate the importance of delirium detection and its impact. Strategies aimed at mitigating the negative effects of delirium on critical care outcomes need to be developed.

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Conflicts of interest

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