Can Intensive Care Unit Delirium Be Prevented and Reduced?

Lessons Learned and Future Directions

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Abstract

Delirium is a form of acute brain injury that occurs in up to 80% of critically ill patients. It is a source of enormous societal and financial burdens due to increased mortality, prolonged intensive care unit (ICU) and hospital stays, and long-term neuropsychological and functional deficits in ICU survivors. These poor outcomes are not only independently associated with the development of delirium but are also associated with increasing delirium duration. Therefore, interventions should strive both to prevent the occurrence of ICU delirium and to limit its persistence.

Both patient-centered and ICU-acquired risk factors need to be addressed early in the ICU course to maximize the efficacy of prevention strategies and to improve long-term outcomes of ICU patients. In this article, we review strategies for early detection of patients who are delirious and who are at high risk for developing delirium, and we present a clinically useful ICU delirium prevention and reduction strategy for clinicians to incorporate into their daily practice.

Keywords: delirium; critical illness; risk factors; prevention; early therapy

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Delirium is a form of acute brain injury that occurs in 60 to 80% of mechanically ventilated ICU patients and 20 to 50% of nonventilated patients (1–5). It is characterized by an acute change or fluctuation in baseline mental status, inattention, and either disorganized thinking or an altered level of consciousness (6). Delirium can significantly decrease survival and worsen quality of life after critical illness through long-term complications such as cognitive impairment, functional impairment, and institutional placement (2, 3, 7). It is the strongest predictor of ICU length of stay,

even after adjusting for factors such as severity of illness and age (8). Furthermore, delirium can be highly distressing for family members and caregivers (9). With an annual cost of \$4 to \$16 billion in the United States alone (10), it is now recognized as a major public health problem (11).

Patients who experience even 1 day of delirium suffer from poor clinical outcomes, namely higher mortality, more days on mechanical ventilation, and more cognitive impairment, and accrue higher ICU and hospital costs (3, 10, 12, 13). It is also important to recognize that

a “dose-dependent” relationship exists between the duration of delirium and poor clinical outcomes. Cohort studies have demonstrated that for each day that an ICU patient is delirious, the risk of 6-month and 1-year mortality increases by 10% and the risk of remaining in the hospital increases by 20% (3, 12). Furthermore, the duration of delirium is an independent predictor of cognitive impairment 1 year after ICU admission (13, 14). Therefore, to limit the long-term consequences of delirium, prevention strategies should strive not only to prevent the development of delirium but also to

reduce its duration in patients already diagnosed with delirium.

Although data on successful strategies to prevent the occurrence of delirium are more limited, multiple high-quality intervention studies to halt and limit the duration of delirium in its earliest stages have successfully reduced the duration of delirium and improved other clinical outcomes. This suggests that despite the occurrence of delirium, strategies to reduce the delirium duration may be the first area of focus for ICU teams (15–20). The efficacy of delirium prevention strategies in critically ill patients may be more difficult to demonstrate given the high prevalence of delirium at the time of ICU admission and the larger studies needed to detect differences in incident delirium (binary outcome) compared with days of delirium (continuous outcome).

In this article, we discuss (1) strategies for early detection of patients with delirium and identification of patients at risk for delirium, and (2) strategies to prevent and reduce ICU delirium. We will also present a practical, evidence-based approach for incorporating these strategies into daily practice. For each of these topics, this report addresses important gaps in knowledge and opportunities for advancing the field of ICU delirium prevention and reduction.

Early Detection of Delirium

Up to 70% of patients are admitted to the ICU with delirium already present (21). As a result, delirium assessments should be part of the ICU admission physical examination and should also be incorporated into the daily work plan. Patients with delirium can be agitated (i.e., hyperactive), but, more commonly, delirious ICU patients are calm or somnolent (i.e., hypoactive) or they alternate between the hyper- and hypoactive states (i.e., mixed) (22). Because the common forms of delirium can be more difficult to detect clinically, up to 76% of delirium can be missed without routine use of a delirium screening tool (23). The 2013 American College of Critical Care Medicine (ACCM) Clinical Practice Guidelines recommend the Confusion Assessment Method-ICU (CAM-ICU) (24) and Intensive Care Delirium Screening Checklist (ISDSC) (25) as the two most valid and reliable tools for delirium screening (26). Both tools have (1) high sensitivity, specificity, and interrater reliability; (2) excellent clinical feasibility in mechanically ventilated critically ill patients; and (3) good predictive validity in research settings (3, 27). In the clinical setting, the sensitivity may be lower, but specificity remains high (28, 29). Although further work is needed to understand better

how training and environment impact delirium detection in the clinical setting, these tools appear to be the best and most feasible options at this time.

Identifying Patients at Risk for Developing ICU Delirium

Although the pathophysiology of delirium is still poorly understood, studies have shown delirium to be a disease-driven process caused by a complex interaction of factors including: (1) baseline or predisposing risk factors unique to each patient, (2) the patient's acute illness and illness-related factors, and (3) ICU environment and treatment-related factors (Figure 1). These risk factors can further be divided into nonmodifiable and modifiable risk factors. Although more than 100 risk factors have been identified in the literature (30), few have consistently remained associated with delirium across different studies after adjusting for confounding variables (26). This is likely due to the different underlying pathophysiology of delirium across study populations (1, 2, 5, 27, 31).

Patient-Level Predisposing Risk Factors

Recent studies have consistently identified cognitive impairment (4, 32), history of

Figure 1. Risk factors for intensive care unit (ICU) delirium.

hypertension (1, 27), and alcohol use (4, 27) as risk factors that significantly increase the risk of delirium in ICU patients. Although advanced age has been identified as one of most significant risk factors outside of the ICU, this association has remained inconsistent across ICU studies (21, 33). Of the predisposing risk factors, only alcohol withdrawal is modifiable. Physiologic dependence from chronic exposure can lead to withdrawal in the setting of abrupt discontinuation of alcohol use. An additional risk factor that has been variably identified in studies is cigarette smoking (1, 4). Because smoking is highly prevalent in critically ill patients (34, 35), it deserves further investigation, because it may be easily modified with nicotine replacement therapy.

Illness-related Risk Factors

High severity of illness at ICU admission (21, 27, 33) has been consistently identified as an independent risk factor for development of delirium in ICU patients. Coma has also been identified as a risk factor for delirium, particularly coma that is medication-induced as opposed to coma that is due to a primary neurologic condition or is illness related (4, 27, 36, 37). Although patients who are mechanically ventilated have a higher prevalence of delirium compared with nonventilated patients, data on the association between respiratory failure and delirium are limited, and results have been inconsistent across studies (1, 4, 21). Possible reasons for the limited data are the exclusion of non-mechanically ventilated patients (31, 37, 38) and lack of measurement of mechanical ventilation as a risk factor in ICU delirium studies (27, 32).

ICU Treatment-related Risk Factors

The influence of ICU-level risk factors on the development and persistence of delirium needs to be stressed because (1) they are all modifiable, (2) reduction of these risk factors is associated with reduced duration of ICU delirium and improvements in clinical outcomes, and (3) these factors are closely interconnected.

Sedative use. The vast majority of mechanically ventilated patients receive sedatives in the ICU. Observational studies have demonstrated that sedative choice and sedative-induced coma (27) are independently associated with an increased risk of delirium. Benzodiazepines appear to be associated with delirium across different

ICU populations and have demonstrated a dose-dependent relationship (21, 31, 33, 39), although a few studies have found no significant relationship (26). Most studies on opiates report an increased risk of delirium, particularly when associated with coma or when used in combination with other sedatives (1, 21, 27). One study showed a decreased risk of delirium (38), possibly because of its use for pain management. Finally, recent studies suggest that use of dexmedetomidine and/or avoidance of benzodiazepines may be associated with a lower risk of delirium. The SEDCOM (Safety and Efficacy of Dexmedetomidine Compared with Midazolam) and MENDS (Maximizing Efficacy of Targeted Sedation and Reducing Neurological Dysfunction) randomized controlled trials showed that mechanically ventilated medical and surgical ICU patients sedated with dexmedetomidine versus benzodiazepines had a 20% lower delirium prevalence (15) and 4 more days alive without delirium and coma (40). Preliminary data in cardiac surgery patients suggest that dexmedetomidine may also be associated with a lower incidence of delirium compared with propofol (41) and shorter duration of delirium compared with morphine (16).

Immobility. ICU delirium and neuromuscular function have been postulated to be closely interconnected (42). Both observational and clinical trial data suggest that immobility is an independent risk factor for delirium in ICU and non-ICU hospitalized patients (4, 18, 39, 42–45).

Preventing and Reducing ICU Delirium—A Practical Approach

Drawing from current evidence, we propose a practical approach for preventing the development of delirium and limiting its duration through a combination of strategies demonstrated to be useful for all ICU patients (ICU-level strategies) and individually titrated interventions (patient-level strategies) (Figure 2).

ICU-Level Strategies

Given the multifactorial nature of delirium and the interdependency of ICU treatment-related risk factors, it is not surprising that multicomponent ICU-level strategies have had better success with reducing the duration of delirium compared with

pharmacologic strategies that address only a few ICU-level risk factors (Table 1, Figure 3). One particular bundled approach in which each individual component is clinically related and evidence-based in high-impact, peer-reviewed articles is called the Awakening and Breathing Coordination, Delirium monitoring, and Exercise/Early mobility or “ABCDE bundle” (46, 47). This approach may decrease the duration of delirium and decrease days on mechanical ventilation (48), and all such bundles should be points of further study in various patient populations. Another pre-post study implementing a protocol to standardize pain, agitation, and delirium management reduced incidence of subclinical delirium, days on mechanical ventilation, ICU and hospital length of stay, and ICU cost (49). We will now review the evidence supporting the use of these nonpharmacologic ICU-level interventions.

Pain management. Most critically ill patients will experience pain during their ICU stay (50), and nearly 50% will experience significant pain (51). Studies suggest that pain may be a risk factor for delirium (27, 31). In addition to the deleterious cognitive effects of pain itself, another possible reason is that pain is a frequent cause of agitation in the ICU, and if it is not recognized, pain can lead to inappropriate sedative administration. Indeed, a cohort study found that ICU patients who were regularly assessed for pain received less sedation, spent fewer days on mechanical ventilation (8 vs. 11 d), and fewer days in the ICU (13 vs. 18 d) compared with those who did not receive pain assessments (52). Another possible reason is that pain medication may be given in excess of what is required for pain control. Therefore, the goal of pain management through routine pain monitoring should be adequate pain control without oversedation and preemptive treatment of pain prior to painful procedures. Because increased vital signs do not always correlate with pain, it is important to use a structured tool for pain monitoring in patients who are unable to communicate, such as the Behavioral Pain Scale (BPS) (51) or the Critical-Care Pain Observation Tool (CPOT) (26, 53).

Agitation management. Agitation is common in critically ill patients, and identification of the underlying cause(s) of agitation is crucial for determining the

Figure 2. A clinically useful delirium prevention and reduction protocol. This proposed approach incorporates principles of intensive care unit (ICU)- and patient-level delirium prevention and reduction assembled from multiple evidence-based sources but has not yet been tested in a critically ill population. *If not contraindicated. CAM-ICU = Confusion Assessment Method-ICU; ISDSC = Intensive Care Delirium Screening Checklist.

appropriate treatment for agitation. Common causes for agitation include pain, delirium, withdrawal from alcohol or chronic opiates or sedatives, factors associated with the acute illness (e.g., hypoxia and hypotension), and anxiety. Treatment of agitation that does not address the underlying cause can incite or prolong delirium (e.g., benzodiazepine given for agitation due to pain), whereas successful treatment or responsiveness to the underlying cause can reduce sedation use and can improve clinical outcomes. A pre-post study showed that routine pain and agitation assessment, coupled with physician notification of untreated pain and agitation, led to more rapid deescalation of analgesic and psychoactive medications and a 50% decrease in duration of mechanical ventilation and nosocomial infections (51).

Sedation management. Sedation-induced coma is associated not only with subsequent ICU delirium but also with other complications of prolonged immobility, such as muscle atrophy and weakness, ventilator dependency, venous

thromboembolic disease, and pressure sores (54–56). Therefore, the goal of sedation in ICU patients should be to achieve a level of wakefulness so patients can participate in reorientation and early mobility interventions. Three different approaches that have demonstrated good outcomes are (1) daily interruption of sedation, (2) targeted light sedation, and (3) no sedation. Although data are insufficient to determine if any of these strategies alter delirium incidence or duration, these strategies are associated with reduced time on the mechanical ventilator and ICU length of stay and decreased mortality and have been demonstrated to be safe, feasible for incorporation into daily care, and acceptable to ICU staff (57–61). At least one, if not all, of these approaches should be adopted into practice to effect a “less is more” culture of sedation use. Routine monitoring of quality and depth of sedation is needed to guide these strategies. The 2013 ACCM Clinical Practice Guidelines (26) recommended the Richmond Agitation-Sedation Scale (RASS) (62) and

Sedation-Agitation Scale (SAS) (63) as the two most valid, reliable, and feasible sedation assessment tools for goal-directed sedation delivery.

Early mobilization. Immobility has been consistently identified as a risk factor for delirium in hospitalized non-ICU patients and in a few ICU-based studies (4, 43). Furthermore, functional disability is a common consequence of delirium (64, 65). Studies in both healthy and diseased non-ICU patients suggest that exercise improves neuropsychiatric outcomes (42). A randomized controlled trial and its subsequent implementation study in mechanically ventilated critically ill adults showed that early implementation of physical and occupational therapy (e.g., passive range of motion in unresponsive patients, active exercises in interactive patients) versus usual care was associated with reduced delirium prevalence (21% vs. 53%) and reduced delirium duration (2 vs. 4 d), was safe and well-tolerated (17, 18), and may lead to cost savings (66). In addition, the intervention group had more days alive off mechanical ventilation

Table 1. Multicomponent intensive care unit-level delirium prevention strategies are associated with improved clinical outcomes

Study Author, Year (Ref)	Light Sedation OR Sedation Interruption	Breathing	Early Exercise	Pain Control	Delirium Assessment	Clinical Outcomes
Girard <i>et al.</i> , 2008 (84)	x	x				Mechanical ventilation ↓ 3 d ICU length of stay ↓ 4 d Mortality ↓ 32%
Morris <i>et al.</i> , 2008 (87)	x	x	x			ICU length of stay ↓ 1.4 d Hospital length of stay ↓ 3.3 d
Schweickert <i>et al.</i> , 2009 (17)	x		x		x	Delirium ↓ 2 d Mechanical ventilation ↓ 2.4 d Independent functional status ↑ 24%
Needham <i>et al.</i> , 2010 (18)	x		x		x	ICU d not delirious ↑ 32% Sedative use and dose ↓ ICU length of stay ↓ 2.1 d Hospital length of stay ↓ 3.1 d
Skrobik <i>et al.</i> , 2010 (49)	x			x	x	Subsyndromal delirium incidence ↓ 8% ICU length of stay ↓ 1 d Mechanical ventilation ↓ 1.3 d Pain ↓ Cost of ICU stay ↓ \$933
Balas <i>et al.</i> , 2013 (48)	x	x	x		x	Delirium ↓ 1 d Mechanical ventilation ↓ 3 d

Definition of abbreviation: ICU = intensive care unit.

(23.5 vs. 21.1 d) and improved return to independent functional status. Of note, patients in both the intervention and control groups in the randomized controlled trial received goal-directed sedation and/or daily interruption of sedatives or narcotics. This suggests that the reduction in delirium duration may be due to early exercise, rather than sedation management.

Sleep promotion. Critically ill patients experience poor sleep quality in the ICU (67, 68). Because sleep deprivation leads to similar clinical and physiologic derangements as delirium, it has been postulated to be a risk factor for ICU delirium (69). A recent quality improvement study incorporating both nonpharmacologic and pharmacologic sleep-promoting interventions in medical ICU patients reduced incident delirium by 20% and reduced delirium duration (19). Several studies in ICU patients with lower severity of illness showed that nonpharmacologic sleep promoting interventions (e.g., earplugs, reducing nighttime procedures and noise) were feasible, reduced subclinical delirium, and improved self-reported sleep quality (70–72). Although further study is

needed in more general ICU populations, given the relative ease of implementation, minimal risk, and potential benefit of these interventions, it would be reasonable to implement them into usual care.

Reorientation. Disorientation due to preexisting cognitive impairment and visual and hearing impairment are risk factors for delirium (4, 32, 73). In hospitalized non-ICU patients, a multicomponent strategy that featured reorientation interventions (e.g., board with names of care team members and day's schedule, cognitively stimulating activities three times daily, visual aids, and hearing protocol) reduced incident delirium by 40% (74). Limited studies in the ICU suggest a similar benefit. A recent pre-post study on a reorientation strategy that included listening to music and reading newspapers reduced incident delirium by 13% in a mixed medical-surgical ICU (20).

Patient-Level Pharmacologic Prevention

Data on preventing and treating ICU delirium at the patient level are mixed. Current evidence suggests a potential

benefit from dexmedetomidine and antipsychotics, but other agents, such as cholinesterase inhibitors and melatonin, have not been found to be helpful in preventing delirium and may even be harmful in the case of cholinesterase inhibitors (75–77). The limited success of these therapies may in part be due to the lack of concurrent multicomponent nonpharmacologic ICU-level delirium prevention strategies.

Sedation with dexmedetomidine. A selective α_2 -adrenoreceptor agonist, dexmedetomidine is a sedative, analgesic, and anxiolytic that is postulated to be associated with less delirium and to promote sleep/wake cycle regulation compared with sustained use of medications that work through the GABA receptor pathway, such as benzodiazepines (78). Several large, well-designed randomized controlled trials comparing dexmedetomidine versus benzodiazepines for sedation in mechanically ventilated medical and surgical ICU patients have shown that dexmedetomidine was associated with a 30% lower prevalence of delirium (15) and more days alive without delirium and coma (7 vs. 3 d) (40). In addition,

Figure 3. Intensive Care Unit (ICU)-level delirium prevention strategies are interconnected. BPS = Behavioral Pain Scale; CPOT = Critical-Care Pain Observation Tool; IV = intravenous.

patients receiving dexmedetomidine were extubated in less time (3.7 vs. 5.6 d) (15), and its use was not associated with increased cost (40). Although evidence comparing dexmedetomidine to other sedatives such as propofol or opiates in the general medical-surgical ICU patient population are more limited (79), these data are encouraging, particularly because there was a demonstrated benefit even in the setting of good sedation practices (e.g., daily sedation vacation, targeted light to moderate sedation level, delirium monitoring). Currently, a large randomized placebo-controlled trial comparing sedation with dexmedetomidine to propofol in a population of mechanically ventilated ICU patients with higher severity of illness is ongoing (Maximizing the Efficacy of Sedation and Reducing Neurological Dysfunction and Mortality in Septic Patients with Acute Respiratory Failure, or MENDS-2 study; Clinicaltrials.gov Identifier NCT 01739933).

The evidence supporting dexmedetomidine for delirium prophylaxis

is less clear. In patients after cardiac surgery, an unblinded RCT suggested that dexmedetomidine may be associated with less incident delirium when compared with propofol or midazolam (41). In a separate study, cardiac surgery patients on dexmedetomidine experienced fewer days of delirium and less time to extubation compared with patients receiving morphine for sedation, but there was no difference in incident delirium (16). Although data are currently insufficient to support the widespread use of dexmedetomidine for sedation in all ICU patients, the 2013 ACCM guidelines recommend that dexmedetomidine could be considered for use as a sedative in patients with delirium and in patients who are at high risk for delirium (26).

Antipsychotics. Typical antipsychotics, such as haloperidol, are hypothesized to treat delirium by blocking dopamine-mediated neuronal excitability and thus stabilizing cerebral function (80). Although they were formerly recommended by major guidelines for treatment of ICU delirium and are still widely used for that indication (81, 82),

no large-scale prospective RCTs have tested the impact of antipsychotics on delirium duration, and the 2013 ACCM guidelines no longer recommend for or against their use. A small trial comparing quetiapine versus placebo in delirious ICU patients who were already receiving haloperidol found that delirium resolved faster in the haloperidol plus quetiapine group compared with the haloperidol plus placebo group (1 vs. 4.5 d) (83). Furthermore, the Modifying the Incidence of Neurologic Dysfunction, or MIND, study showed that antipsychotics (haloperidol and ziprasidone) were feasible to administer in mechanically ventilated ICU patients (84). Currently, a large randomized placebo-controlled trial testing their efficacy in a diverse population of mechanically ventilated ICU patients is ongoing (Modifying the Impact of ICU-Associated Neurological Dysfunction—USA, or MIND-USA; Clinicaltrials.gov Identifier NCT01211522).

The efficacy of antipsychotics for delirium prophylaxis has been suggested in two studies on postoperative delirium

Table 2. Intensive care unit delirium—implications for clinical care

Delirium is a source of significant morbidity and mortality in critically ill patients. Although 1 d of delirium is associated with poor outcomes, a longer duration of delirium is associated with even worse outcomes.

Early identification of patients at risk for developing delirium and of patients with delirium is imperative for effective delivery of preventative and therapeutic interventions. Delirium assessments should be part of the ICU admission physical examination and should be incorporated into the daily work plan.

Modifiable patient-centered risk factors for delirium should be recognized and treated.

ICU-acquired risk factors are potentially modifiable and are closely interconnected.

Multicomponent strategies can effectively limit these risk factors, and integration of these strategies into daily ICU practice can shorten the duration of ICU delirium and improve clinical outcomes.

Pharmacologic prevention and treatment for delirium (e.g., dexmedetomidine over benzodiazepines for sedation, antipsychotics) can be considered for individual patients, although the efficacy of these strategies is still unclear.

Definition of abbreviation: ICU = intensive care unit.

prophylaxis in elective surgery patients: one using low-dose haloperidol versus placebo (85) and one using a single dose of risperidone versus placebo (86). Because these studies involved patients with a low severity of illness, they may not be generalizable to broader ICU populations.

Conclusions

As advances in critical care have increased survival, greater attention is being placed on the prevention and reduction of long-term complications of critical illness. ICU delirium is a disorder that can have

a profound negative impact on survivors of critical illness and their families. Recent years have brought significant advances in our understanding of risk factors for delirium and have resulted in effective ICU-level strategies that have reduced the adverse impact of delirium, such as targeted sedation and early mobilization. Nevertheless, there is still much work to be done in this field. Monitoring for delirium is still inconsistent, and implementation of these ICU-level processes of care is not routinely practiced. There is also limited research assessing the optimal approach to using pharmacologic and multicomponent nonpharmacologic strategies to prevent the onset and reduce the duration of delirium in the ICU. Fortunately, ongoing studies, such as the MIND-USA trial, should help clarify some of these questions. Key points associated with this review are found in Table 2. ■

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