Prevention, Recognition, and Management of Delirium in the Intensive Care Unit

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The intensive care unit (ICU) can be a stressful and intimidating environment for critically ill patients. Behavioral disturbances in critically ill patients may be detrimental to the safety of patients and the nurses caring for these patients. These disturbances may manifest as ICU delirium. The development of ICU delirium can lead to dire consequences, such as an increased risk of 6-month mortality, extended ICU and hospital lengths of stay, and long-term cognitive impairment.1–4 Critical care nurses caring for delirious patients are often the first to notice any changes in mental status or behavior; therefore, it is important for critical care nurses to have an understanding of ICU delirium. This review focuses on the prevention and recognition of delirium and provides an overview of both nonpharmacological and pharmacological methods of managing ICU delirium.

What Is ICU Delirium?

Delirium is derived from the Latin word de lira, meaning “off the path.” Several older terms have been used to describe ICU delirium and are synonymous; these terms include sundowning, acute confusional state, ICU encephalopathy, ICU psychosis, and ICU syndrome. The Diagnostic and Statistical Manual of Mental Disorders, Version 4 defines delirium as a disturbance in level of consciousness, with a noted change in cognition, that develops over a short period of time (hours to days) and fluctuates over the course of a day.5 The incidence of ICU delirium has been noted to range from 15% to 80%, depending on the assessment tool used and the population studied.1–9

Research evaluating the pathogenesis of delirium is in its infancy; however, neurotransmitter imbalances are thought to play a major role in the development of ICU delirium—specifically, a decrease in acetylcholine and an increase in dopamine in the brain of patients with ICU delirium.9 Other proposed mechanisms include inflammation, impaired oxidative metabolism, and availability of large neutral amino acids. Discussions on these mechanisms of injury are beyond the scope of this review, and readers are referred to a recent review on the topic.9

What Are the Clinical Consequences of ICU Delirium?
The negative impact of ICU delirium on clinical outcomes has been well described in the medical literature. In a landmark trial investigating ICU delirium in 275 adult medical and coronary ICU patients, Ely and colleagues1 noted that the...
incidence of delirium during an ICU stay was associated with a higher 6-month mortality rate (34% vs 15%, \( P = .03 \)) and a 3-fold relative increase in 6-month mortality, compared with those in whom delirium never developed \( (hazard \ ratio = 3.2, 95\% \ confidence \ interval = 1.4–7.7, \ P = .008) \). Delirious patients were also noted to have a 10-day longer hospital length of stay than patients without delirium. A study evaluating 134 surgical and trauma ICU patients found that delirious patients required a greater duration of mechanical ventilation (9.1 vs 4.9 days, \( P < .01 \)) and had longer ICU (12.2 vs 7.4 days, \( P < .01 \)) and hospital stays (20.6 vs 14.7 days, \( P < .01 \)), respectively.

The negative consequences of ICU delirium are not confined to a particular hospital admission. Development of long-term cognitive impairment including increased transition to dementia after ICU discharge has also been demonstrated in the medical literature. Using a battery of cognitive examinations, Girard and colleagues\(^6\) investigated the relationship between duration of delirium and development of long-term cognitive impairment and noted that an increase from 1 day of delirium to 5 days was independently associated with a decline in cognitive function at 3-month follow-up. Jackson and coinvestigators\(^4\) reported that delirium in non-ICU patients was associated with cognitive decline over 1 to 3 years after hospital discharge. In addition, the length of delirium has been shown to negatively impact clinical outcomes in patients with ICU delirium. Pisani and colleagues\(^10\) investigated the duration of delirium and 1-year mortality in 304 medical ICU patients. For each additional day of delirium, the risk of 1-year mortality increased by 10% \( (hazard \ ratio = 1.10, \ P = .01) \). Not surprisingly, ICU delirium also has been noted to be an independent risk factor for increased ICU and hospital costs, with a median increase approaching $10,000 and $15,000, respectively.\(^11\)

### What Are the Risk Factors for Development of ICU Delirium?

Many risk factors exist for the development of ICU delirium.\(^12\)–\(^14\) These risk factors can be delineated into 2 distinct categories: predisposing and precipitating. Predisposing risk factors are often present at ICU admission, are less modifiable, and are a function of the patient’s overall health status before ICU admission. In contrast, precipitating risk factors are those risk factors that are not present at ICU admission and may be most modifiable. Table 1 lists the predisposing and precipitating risk factors for ICU delirium. Modification of these risk factors should play an integral role in the management of ICU delirium. Potentially, the most modifiable risk factor is the use of medications, including benzodiazepines and opioids, that potentiate the development of delirium.

Pandharipande and coworkers\(^13\) sought to elucidate the relationship between the use of sedatives and analgesics and the risk of development of ICU delirium in medical and coronary ICU patients. The use of lorazepam was identified as an independent risk factor for the daily development of ICU delirium \( (odds \ ratio = 1.2, 95\% \ confidence \ interval = 1.1–1.4, \ P = .003) \). The risk of ICU delirium developing was high even at low doses and plateaued at relatively higher doses (approximately 20 mg lorazepam per day), which can easily be exceeded in ICU patients receiving doses greater than 1 mg/h. Figure 1 illustrates the relationship between daily lorazepam dose and risk of developing ICU delirium. In a separate study completed in trauma/surgical patients by Pandharipande and colleagues,\(^14\) midazolam was identified as a risk factor for development of ICU delirium \( (odds \ ratio = 2.5, \ P = .002) \). The use of opioids as a risk factor for ICU delirium is less clear, with conflicting data present. Other medications that have been implicated as risk factors for ICU delirium are depicted in Table 2. Modification

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**Table 1: Predisposing and Precipitating Risk Factors for the Development of Intensive Care Unit Delirium**

<table>
<thead>
<tr>
<th>Predisposing Risk Factors</th>
<th>Precipitating Risk Factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline dementia</td>
<td>Medications</td>
</tr>
<tr>
<td>Advanced age</td>
<td>Dehydration</td>
</tr>
<tr>
<td>Depression</td>
<td>Acute infection/sepsis</td>
</tr>
<tr>
<td>Injury severity</td>
<td>Seizures</td>
</tr>
<tr>
<td>Chronic illness (ie, hypertension)</td>
<td>Hyperthermia</td>
</tr>
<tr>
<td>Tobacco/alcohol use</td>
<td>Withdrawal syndromes</td>
</tr>
<tr>
<td>Visual/hearing impairment</td>
<td>Metabolic disturbances</td>
</tr>
<tr>
<td>ApoE4 polymorphism</td>
<td>Head trauma</td>
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ous subtypes of delirium in medical ICU patients. The incidence of purely hyperactive delirium was noted in only 1.6% of patients. Pure hypoactive delirium was observed in 43.5% of patients, with 54.1% of patients having a mixed delirium subtype. These findings are important to note, as the majority of patients did not display overt signs of aggression and agitation, signifying the importance of routine screening for ICU delirium.

Some patients may exhibit only some signs of delirium, which is referred to as subsyndromal delirium. Ouimet and colleagues used the Intensive Care Delirium Screening Checklist (ICDSC) to determine whether the incidence of subsyndromal delirium was related to any adverse events compared with patients who exhibited no signs of delirium. The study evaluated 604 patients and stratified them into 3 categories: “no delirium,” “subsyndromal delirium,” and “clinical delirium.” Intensive care unit mortality rates in the groups were 2.4%, 10.6%, and 15.9%, respectively. The difference between “no delirium” and “subsyndromal delirium” was statistically significant (P = .002). Interestingly, there was no statistical difference between “subsyndromal delirium” and “clinical delirium.” The results of this study are important because they show that ICU delirium is not an all-or-none phenomenon. Rather, ICU delirium is a disease spectrum with ICU delirium on one extreme end of the spectrum and normal mentation on the other extreme end, with subsyndromal delirium in the middle.

What Are the Different Types of ICU Delirium?
Delirium in the ICU can be stratified into 3 main types—hypoactive, hyperactive, and mixed, in which patients exhibit signs of both hypoactive and hyperactive delirium. Table 3 lists the common signs of hypoactive and hyperactive delirium. Hyperactive delirium is the easiest type of delirium to identify for nurses and ICU clinicians. However, its true incidence in the ICU is low. Peterson and colleagues investigated the various subtypes of delirium in medical ICU patients. The incidence of purely hyperactive delirium was noted in only 1.6% of patients. Pure hypoactive delirium was observed in 43.5% of patients, with 54.1% of patients having a mixed delirium subtype. These findings are important to note, as the majority of patients did not display overt signs of aggression and agitation, signifying the importance of routine screening for ICU delirium.

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What Are the Different Screening Tools Used to Identify ICU Delirium?
Delirium screening in the ICU can be hampered by the inability of patients who are intubated to communicate effectively. To this end, various screening tools to identify delirium in the critically ill patient have been created and
validated. Of these tools, the Confusion Assessment Method for the Intensive Care Unit (CAM-ICU)\(^3\) and the ICDSC\(^17\) are the most studied and validated screening tools in clinical practice today.

The CAM-ICU considers 4 different components of ICU delirium: (1) acute onset of symptoms or fluctuating course, (2) inattention, (3) disorganized thinking, and (4) altered level of consciousness. For a patient to be deemed delirious or “CAM-positive,” components 1 and 2 must be present, plus either component 3 or 4. The CAM-ICU also involves the use of visual and/or verbal cues to assess for the presence of delirium.

The ICDSC is an 8-item questionnaire that assesses delirium using the Diagnostic and Statistical Manual of Mental Disorders, Version 4 criteria for delirium and other hallmark features of delirium. The ICDSC evaluates level of consciousness, inattention, disorientation, hallucination, psychomotor agitation or retardation, inappropriate speech or mood, sleep/wake cycle disturbances, and symptom fluctuation. Points are assigned for any abnormalities present, and an ICDSC score of 4 or more indicates clinical delirium.

Potential barriers to assessment include lack of knowledge of ICU delirium, unfamiliarity with assessment tools, confusing terms in the assessment tools, lack of time to complete assessment, and lack of clarity about who should assess for delirium. These barriers can complicate and delay proper recognition and treatment of delirium, potentially placing patients at increased risk for development of negative sequelae, as described earlier.

**What Are the Nonpharmacological Options for the Prevention and Management of ICU Delirium?**

Once a patient has been diagnosed as delirious, clinicians should look to optimize and remove any risk factors for delirium. Reorienting patients by providing visual and hearing aids is helpful in reducing delirium. Environmental risk factors are relatively easy to correct, and they should be addressed before pharmacological treatment is considered. Mobilization early in the hospital stay can help to reduce ICU delirium. Sleep promotion may play an important role in the management of patients with ICU delirium. Sleep promotion and improving sleep hygiene include reestablishing routine sleep/wake cycles in patients by promoting lights on during the day and off at night to mimic natural conditions and instituting quiet times at bedtime. In a small study of surgical ICU patients, Aurell and Elmqvist\(^18\) found that patients slept for only approximately 2 hours per day, of which only 6% was rapid-eye-movement sleep. Sleep deprivation can cause pathophysiological changes, which may lead to multiorgan failure, which can precipitate or aggravate delirium. Protocolized multicomponent interventions, including early mobilization with range-of-motion exercises and the use of visual/hearing aids, have been shown to reduce the incidence of delirium.\(^19\)

In addition, judicious use of medications known to potentiate delirium may reduce ICU delirium. However, this is a fine line as many patients in the ICU require sedative and analgesic medications for comfort. Minimizing the use of sedative agents such as benzodiazepines, if possible, along with daily sedation holidays may decrease the amount of sedatives and analgesics.\(^20\)

**What Are the Pharmacological Options for the Management of ICU Delirium?**

If nonpharmacological means are ineffective at managing ICU delirium, pharmacological methods may need to be used. Various agents have been used to manage ICU delirium, with haloperidol and atypical antipsychotics being used most often. In 2001, Ely and associates\(^21\) surveyed 912 health care professionals regarding management of ICU delirium. They noted that 66% of health care professionals used haloperidol to treat ICU delirium, 4% used atypical antipsychotics, and 18% used sedatives, including benzodiazepines and propofol. In a follow-up study in 2009, Patel and colleagues\(^22\) noted that 86% of responding health care professionals reported using haloperidol to manage ICU delirium, whereas approximately 40% reported using atypical antipsychotics.

**Haloperidol**

Haloperidol is a typical antipsychotic with a poorly defined mechanism of action in the setting of ICU delirium. It is thought to exert its mechanism of activity to stabilize cerebral activity by acting as a dopamine-2 receptor antagonist and reducing dopaminergic activity at the cerebral synapses and basal ganglia. In 2002, guidelines from the Society of Critical Care Medicine regarding sedative and analgesic use in critically ill patients\(^2\) recommended...
the use of haloperidol to manage ICU delirium. Haloperidol is not without risks, including the development of dose-dependent QT prolongation and extrapyramidal symptoms (EPS). It is important to identify patients with a history of cardiac disease before using haloperidol, because it has been reported to predispose patients to QT prolongation. Incidence of torsade de pointes due to haloperidol is not well defined; however, one study suggests that it may be 3.6%, which further underscores the need for accurate histories and close monitoring, especially for those patients at risk, including those receiving medications known to prolong the QT interval, such as fluoroquinolones and certain antiarrhythmics.

Extrapyramidal symptoms are also a noted adverse event of haloperidol; these symptoms occur as a result of an active metabolite of haloperidol. Typical manifestations of EPS include akathisia, dystonia, pseudoparkinsonism, and dyskinesia. The development of EPS is likely related to haloperidol’s effects on dopamine. Extrapyramidal symptoms have been reported less frequently with intravenous administration than with oral administration. Extrapyramidal symptoms are usually a self-limiting disorder that can last for up to 2 weeks with treatment, including discontinuation of haloperidol and administration of diphenhydramine or benztropine.

Another rare but potentially life-threatening adverse event associated with the use of haloperidol and other antipsychotics is neuroleptic malignant syndrome, which is characterized by muscle rigidity, elevated creatine kinase levels, and fever (>38°C). If neuroleptic malignant syndrome is suspected, discontinuation of the antipsychotic and initiation of dantrolene are recommended. Haloperidol dosing strategies may vary widely, from intermittent bolus dosing to scheduled bolus dosing and continuous infusions. These strategies have been used in clinical practice with various results. Wide dosage ranges of haloperidol have been used; however, the optimal dosing strategy is poorly defined.

Atypical Antipsychotics
Atypical antipsychotics such as olanzapine, ziprasidone, and quetiapine have largely replaced typical antipsychotics such as haloperidol for the treatment of schizophrenia because of their similar efficacy and reduced adverse effect profile. Recently, they have been studied as possible alternatives to haloperidol for managing ICU delirium, with each showing promising results.

The mechanism of action of atypical antipsychotics for ICU delirium has not been fully elucidated; however, their proposed mechanism is believed to be related to their effects on neurotransmitter balance. Atypical antipsychotics are not without their potential pitfalls, including drowsiness, QT interval changes, and EPS. However, the risk is much lower in comparison to haloperidol. Atypical antipsychotics also may produce metabolic changes, including weight gain and new onset diabetes. However, this phenomenon is primarily seen with long-term use. Dosing, adverse events, and monitoring parameters for the antipsychotic agents used in ICU delirium are described in Table 4.

Dexmedetomidine
Dexmedetomidine is a centrally acting alpha2a agonist, producing sedative effects rapidly. Dexmedetomidine also produces anxiolytic and mild analgesic effects. The use of dexmedetomidine as a sedative agent in the ICU has increased substantially, because of some of its benefits, including minimal impact on respiratory drive and proposed predictability. Another potential benefit in the setting of ICU delirium is its γ-aminobutyric acid–sparing mechanism of action compared with benzodiazepines. In a study evaluating dexmedetomidine and lorazepam for sedation in 106 medical and surgical ICU patients, Pandharipande et al reported more delirium/coma-free days in the dexmedetomidine group (7.0 vs 3.0 days, P = .01). In a separate study comparing dexmedetomidine with midazolam in 375 medical and surgical patients, Riker et al reported that the percentage of patients with delirium was lower in the dexmedetomidine group (54% vs 76%, P < .001). These results are promising and give insight into the potential role of dexmedetomidine in ICU delirium. Evidence for use of dexmedetomidine as a treatment of ICU delirium is lacking; thus, dexmedetomidine should not be used as a primary treatment option for ICU delirium but rather as a sedative alternative to benzodiazepines to possibly reduce the incidence of ICU delirium.

Summary and Conclusion
Critical care nurses play an important role in preventing delirium by using nonpharmacological means and are in the best position to determine whether patients are delirious. Early recognition of delirium is important, and the use of validated screening tools for ICU
Table 4: Pharmacological Treatment Options for ICU Delirium

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>Adverse Events</th>
<th>Monitoring Parameters</th>
</tr>
</thead>
<tbody>
<tr>
<td>Haloperidol (Haldol)</td>
<td>2 mg IV × 1, may repeat every 15 to 20 min, doubling the dose each time until agitation resolved (once resolved, use this dose as maintenance dose every 4 to 6 h)</td>
<td>EPS, QT prolongation, sedation, tardive dyskinesia (rarely), NMS</td>
<td>Electrocardiograph, complete blood cell count, vital signs, muscle rigidity</td>
</tr>
<tr>
<td>Olanzapine (Zyprexa)</td>
<td>2.5–5.0 mg orally daily</td>
<td>EPS, QT prolongation, sedation, tardive dyskinesia (rarely), NMS, hyperglycemia</td>
<td>Electrocardiograph, complete blood cell count, vital signs, muscle rigidity</td>
</tr>
<tr>
<td>Ziprasidone (Geodon)</td>
<td>40 mg orally every 6–12 h</td>
<td>EPS, QT prolongation, sedation, tardive dyskinesia (rarely), NMS, hyperglycemia</td>
<td>Electrocardiograph, complete blood cell count, vital signs, muscle rigidity</td>
</tr>
<tr>
<td>Quetiapine (Seroquel)</td>
<td>50 mg orally every 12 h (may titrate up to 300 mg every 12 h)</td>
<td>EPS, QT prolongation, sedation, tardive dyskinesia (rarely), NMS, hyperglycemia</td>
<td>Electrocardiograph, complete blood cell count, vital signs, muscle rigidity</td>
</tr>
<tr>
<td>Dexmedetomidine</td>
<td>0.2–1.5 mcg/kg/h IV</td>
<td>Hypotension, bradycardia</td>
<td>Vital signs, level of sedation</td>
</tr>
</tbody>
</table>

Abbreviations: EPS, extrapyramidal symptoms; ICU, intensive care unit; IV, intravenous; NMS, neuroleptic malignant syndrome.

Delirium is key to identifying and initiating treatment of ICU delirium. When prevention and nonpharmacological interventions are ineffective, medications may be used. Improved prevention, recognition, and treatment of ICU delirium can improve outcomes in critically ill patients.

REFERENCES

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