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ICU Delirium: Diagnosis, Risk Factors, and Management

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Abstract Intensive care unit delirium is a complex problem associated with significant negative consequences on patient outcomes. Delirium is also known as acute brain dysfunction, reflecting the evolving paradigm that it is a manifestation of acute organ dysfunction in the setting of neurotransmitter imbalances, inflammation, and metabolic derangements. In recent years, strides have been made towards better understanding its management, although much work remains to be done. Here we review the current state of knowledge regarding diagnosis, pathophysiology, risk factors, prevention, and management as supported by recent literature and the 2013 clinical practice guidelines on pain, agitation, and delirium.

Keywords Intensive care unit · Critical care · Delirium · Encephalopathy · Acute brain dysfunction

Introduction

Delirium has come to be recognized as a major issue in critical care medicine with a significant impact on morbidity and even mortality. Its incidence ranges from 16 to 87 % [1, 2], with mechanically ventilated patients having a higher incidence at up to 60–80 % [3]. Delirium is associated with a longer duration of mechanical ventilation, longer ICU stay, longer hospital stay, increased use of physical restraints, and increased incidence of tracheostomies [4]. It is an independent risk factor for hospital mortality [odds ratio (OR) 2.673, $p < 0.001$], mortality at 6 months (OR 2.562, $p < 0.001$), and dependency in personal activities of daily living (ADL) post-discharge (OR 2.188, $p < 0.046$) [5]. Even up to 12 months following their illness, patients with delirium report a greater decline in physical function, vitality, social function [5], and worse ADL and motor-sensory function scores [6]. With increased awareness of the incidence and consequences of delirium has come management updates and practice changes. In 2013, the American College of Critical Care Medicine (ACCM) updated their clinical practice guidelines on the management of ICU delirium; many of the statements and recommendations will be reviewed below, as well as more recent evidence published since the creation of these guidelines.

Diagnosis

Delirium has several cardinal features: altered level of consciousness, decreased ability to focus, shift, or sustain attention, and either change in cognition or development of a perceptual disturbance [7••]. Delirium can present as hyperactive, hypoactive, or mixed subtypes. Hyperactive delirium tends to present more as hallucinations, delusions, agitation, and restlessness. Hypoactive delirium is characterized by decreased responsiveness, slowed motor skills, withdrawn behavior, and lethargy. Mixed delirium shows characteristics of both types. One prospective study of

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adult medical ICU patients found the incidence of subtypes as 54.9 % mixed, 43.5 % hypoactive, and 1.6 % hyperactive [8].

The 2013 ACCM guidelines recommend routine monitoring of ICU patients for delirium with a suggested frequency of at least once per nursing shift [7••]. Since delirium usually presents with a waxing and waning course, less frequent screening, or screening only on ICU admission, may miss identifying later-onset delirium [9]. The Confusion Assessment Method for the ICU (CAM-ICU) and the Intensive Care Delirium Screening Checklist (ICDSC) are the recommended screening tools [7••, 10, 11]. The ICDSC components are summarized in Table 1; the CAM-ICU and many other excellent resources on ICU delirium can be found online at http://www.icudelirium.org.

Both the CAM-ICU and the ICDSC have been well validated as reliable tools for the diagnosis of delirium, with each having its strengths and weaknesses. The CAM-ICU is based on Diagnostic and Statistical Manual of Mental Disorders (DSM)-III criteria and modified for nonverbal patients. It is designed so that general clinicians can identify delirium rather than rely on psychiatric consultation. The CAM-ICU has been validated in multiple studies against DSM-IV criteria as detecting early delirium with both high sensitivity and specificity [12]. One caveat to using this diagnostic tool is that the patient cannot be deeply sedated for proper assessment.

The ICDSC is designed based on DSM-IV criteria and queries a broader range of symptoms than the CAM-ICU. In contrast to the CAM-ICU, the ICDSC is a slower test to administer, but whereas the CAM-ICU assesses for delirium only at the time of evaluation, the ICSDC takes into account symptom progression over the past 24 h [9]. Both tests have shown significant agreement when compared with one another with good specificity, but operator training can impact the sensitivity to a certain degree. Untrained bedside ICU nurses using these screening tools have demonstrated variability in sensitivity, but with minimal training it appears much of this variability can be minimized [13]. Despite the reproducibility of the results using these tests, clinicians should bear in mind that there will still be a subset of patients for whom the results may be inconclusive, and psychiatric consultation may be warranted for a full DSM-IV-based evaluation.

Pathophysiology

The exact pathophysiology of delirium is not yet well defined, but multiple pathways have been implicated. A combination of drug toxicity, inflammation, and the acute stress response in severe illness is often discussed, with studies focusing on specific neurotransmitters or biomarkers involved in these responses [2]. Imbalances in the cholinergic and dopaminergic systems have been of particular interest in the development of delirium. Acetylcholine transmission affects arousal, attention, memory and rapid eye movement sleep [14, 15]. Additionally, it is involved in downregulating inflammation, and an imbalance of inflammatory markers has been associated with increased risk of delirium [1]. These actions of acetylcholine may explain why anticholinergic medications can lead to iatrogenic delirium [1]. Increased dopaminergic activity has also been implicated as another potential mechanism for the development of delirium. Impaired

Table 1 The intensive care delirium screening checklist

Patient evaluation	Day 1	Day 2	Day 3	Day 4	Day 5
Altered level of consciousness* (A–E)					
If A or B do not complete patient evaluation for the period					
Inattention					
Disorientation					
Hallucination–delusion–psychosis					
Psychomotor agitation or retardation					
Inappropriate speech or mood					
Sleep/wake cycle disturbance					
Symptom fluctuation					
Total score (0–8)					

* Level of consciousness:
A: No response, score: None
B: Response to intense and repeated stimulation (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

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metabolic conditions can lead to excess dopamine levels in the brain due to increased dopamine production and decreased reuptake [15]. Some drugs (for example, buproprion) that increase dopamine activity have been associated with delirium, and conversely, genetic mutations leading to decreased cerebral dopamine activity have been demonstrated to decrease the risk of developing delirium [1]. Other neurotransmitters and markers potentially associated with delirium include serotonin, histamine, cortisol, GABA, glutamate, norepinephrine, and tryptophan [1, 2, 15].

Risk Factors

Many potential risk factors for delirium have been identified; they can be divided into predisposing (baseline) risk factors and precipitating (hospital-based) risk factors, with some further stratifying risk factors into medication-related, environmental, chronic pathology, or patient-specific risk factors [2]. It is important to note the difference in type of risk factor as precipitating risk factors may be targets for intervention. The 2013 ACCM guidelines have highlighted four baseline and two acquired risk factors for the development of delirium: pre-existing dementia, history of hypertension, history of alcoholism, high severity of illness at admission as well as coma and benzodiazepine use [7••]. The baseline factors as well as coma were singled out due to their being positively, independently, and significantly associated with delirium in two or more multivariate analyses. When examining medication-related risk factors for the development of delirium, benzodiazepines were at best found to have no association with delirium, or at worst found to be strongly associated with delirium. Based on these findings, the 2013 guidelines concluded that benzodiazepines may be a risk factor for the development of delirium.

Other risk factors not highlighted in the 2013 ACCM guidelines include increasing age, APOE-4 genotype, tobacco use, and depression for baseline risk factors [3], mechanical ventilation, number and type of medication infusions, anemia, hypotension, metabolic disturbances, lack of daylight, lack of visitors, isolation, immobility, and disturbed sleep cycle for potentially modifiable precipitating risk factors [2, 3]. The large number of risk factors found to contribute to delirium demonstrates the complexity of the pathophysiology of delirium and the heterogeneity in the studies published.

Efforts have been made towards developing prediction tools for ICU delirium with the thought that early identification of those at highest risk for delirium may allow for preventative interventions to be directed in an efficient and cost-effective manner as well as sparing lower risk patients from the potential harms of delirium prevention therapies (e.g., antipsychotics) [16]. An easily obtainable biomarker that has been researched is C-reactive protein (CRP). Delirium is considered to be at least partially inflammatory in etiology; supporting this hypothesis is the finding that inflammatory markers such as interleukin 1 (IL-1), tumor necrosis factor alpha (TNF-α), and interleukin 8 (IL-8) are associated with the development of delirium [17]. Since CRP is also associated with inflammation but more readily obtained, researchers hypothesized and confirmed that it too is a biomarker for delirium. In a prospective observational study of mixed bed ICU patients, CRP assessed on ICU admission was independently associated with an increased risk of delirium [17]. Moreover, every 10 mg/L increase in CRP was associated with a 7 % increase in risk of delirium [17].

Other delirium prediction tools have been in development in the Netherlands and Europe for several years and show promise. E-PRE-DELIRIC and PRE-DELIRIC were developed to predict the development of delirium at time of ICU admission and after 24 h of ICU admission, respectively [16, 18]. Available as an app, these calculators give a single risk prediction value based on routinely collected information. E-PRE-DELIRIC uses age, history of cognitive impairment, history of alcohol abuse, BUN at time of ICU admission, urgency of admission, admission category (MICU, SICU, trauma, etc.), MAP at time of ICU admission, use of corticosteroids, and respiratory failure [16]. PRE-DELIRIC uses information collected after 24 h of ICU admission (age, APACHE-II score, urgency of admission, admission category [MICU, SICU, trauma, etc.], sedation and morphine use, urea level, and presence or absence of infection, coma and metabolic acidosis) [18]. Both have calculators have been validated at multinational sites; however, as sedation and delirium prevention protocols are unstandardized among hospitals, the positive predictive value of these models may change.

Prevention

Although many pharmacologic and nonpharmacologic interventions for the prevention of ICU delirium have been identified and studied, few have clearly proven to be of benefit. The National Institute for Health and Clinical Excellence in the United Kingdom has outlined several interventions to prevent delirium, including assessing for and addressing modifiable precipitating risk factors for delirium (e.g., multiple medications, metabolic disturbances, pain, immobility, and sleep disturbances), keeping a patient's care team members as well as environment the same (e.g., not changing their room), and using nonpharmacologic means preferentially to comfort and reassure

patients who appear in distress, rather than initially using medication [19•]. In contrast, the only intervention explicitly recommended by ACCM guidelines for prevention of delirium is early mobility [7••]. Several studies have been conducted on the mobilization of ICU patients, all demonstrating that it is safe and well tolerated [20–22]. These studies have been conducted both in MICUs and SICUs, examining both spontaneously breathing and mechanically ventilated patients. A randomized-controlled trial of mobilization within the first three days of mechanical ventilation showed that patients receiving the intervention of early PT and OT had a shorter duration of delirium both in the ICU (2 vs. 4 days, $p = 0.03$) and in the hospital (2 vs. 4 days, $p = 0.02$) [20]. Similar results were found in before and after studies [21, 22], with one institution showing not just a decrease in duration but also a decrease in rate of delirium [22]. Furthermore, additional benefits to a program of early mobilization were found, including improved functional outcomes as well as decreased time of mechanical ventilation, ICU LOS, hospital LOS, hospital readmission, and even one-year mortality [20–23].

Regarding pharmacologic interventions directed at ICU delirium prevention, data are either too conflicting or not robust enough to draw definitive conclusions. A 2015 systematic review of clinical trials and cohort studies of medications to prevent ICU delirium concluded that of the studied medications (dexmedetomidine, haloperidol, risperidone, clonidine, dexamethasone, rivastigmine and statins), only antipsychotics for SICU patients and dexmedetomidine for mechanically ventilated patients were associated with reductions in the prevalence of delirium [24]. However, because these trials were not of sufficiently high quality, ACCM guidelines provide no recommendation on dexmedetomidine and in fact suggest against the use of antipsychotics (haloperidol or atypicals) for prophylaxis [7••]. Since the publication of these guidelines, data have continued to be conflicting. Hope-ICU, a randomized, double-blind, placebo-controlled trial examined the prophylactic use of haloperidol in 141 mechanically ventilated medical and surgical ICU patients and concluded that haloperidol did not modify the prevalence or duration of delirium in this population [25]. A 2013 meta-analysis also examined the use of antipsychotics compared to placebo for the prophylaxis of delirium; five trials—all in elderly perioperative patients—met the inclusion criteria of being randomized and placebo controlled [26]. The pooled analysis found a 50 % reduction in the relative risk of delirium [RR (95 % CI) 0.51 (0.33–0.79); $p = 0.01$] when using prophylactic antipsychotics, with no statistically significant or serious adverse outcomes [26]. These findings suggest a role for the short-term use of antipsychotic medications in elderly at risk of delirium; however, the narrow focus of these studies was only on perioperative patients and delirium in the postoperative course. The findings would not be generalizable beyond postoperative ICU patients, but certainly pave the way for further investigation.

The 2013 ACCM guidelines provide no recommendation on pharmacologic or combined pharmacologic and nonpharmacologic prevention protocols [7••]. Indeed, when examining the data on pharmacologic or combined protocols, it is difficult to draw conclusions due to heterogeneous bundles as well as conflicting outcomes. The two most promising protocols are the early awakening, breathing, delirium screening and early exercise (ABCDE) bundle and the pain, agitation and delirium (PAD) management bundles based on current evidence and recommendations (e.g., targeting a light target level of sedation, analgesia-first sedation, etc.) [27•]. The ABCDE bundle aims to address many of the risk factors of delirium using target-based sedation protocols, spontaneous breathing and awakening trials, and early mobilization [28•]. In a before and after study investigating the implementation of the ABCDE bundle in MICU and SICU patients, researchers found that the odds of delirium were markedly reduced (OR 0.55, 95 % CI 0.33–0.93, $p = 0.03$) without significant differences in adverse events such as self-extubations or reintubations [28•]. In a before and after study on a PAD bundle implemented in MICU and SICU patients, rates of delirium remained the same (24.7 vs. 34.2 % pre and post, respectively); however, rates of iatrogenic coma dropped from 20.5 to 8.7 % ($p < 0.0001$) and subsyndromal delirium—defined as an ICDSC score of 1 to 3—were also reduced (33 % pre vs. 24.6 % post, $p = 0.009$) [29]. It is possible that the delirium present in comatose patients pre-implementation became unmasked post-implementation (thus resulting in little change in overall delirium rates between the two groups). In another PAD bundle study in MICU and SICU patients in which the PAD bundle was compared to usual care in a prospective, randomized-controlled trial, delirium incidence in the intervention group receiving PAD bundled care was decreased compared with historic controls (8.5 vs. 18 %) [30]. Unfortunately, the authors were unable to compare delirium incidence to the actual control arm because as per ICU routine in "usual care," delirium incidence was not measured.

Other bundles integrating various combinations of pharmacologic protocols, sleep enhancement protocols and awakening and breathing trials have yielded positive outcomes (e.g,. decreased sedation, decreased duration of mechanical ventilation, etc.) but have had either no effect on delirium incidence [31, 32] or strangely in one study of a protocol minimizing benzodiazepines in favor of dexmedetomidine—an increase in delirium prevalence (81 vs. 93 %, $p = 0.013$) [33]. A systematic review on ICU

delirium bundles concluded that creating an integrated management protocol with a higher number of individual elements (at least six different prevention strategies), such as the PAD or ABCDE bundles, may improve clinical outcomes such as mortality and hospital length of stay, but did not appear to be associated with decreased incidence of delirium [34].

Treatment

Similar to the prevention of delirium, many interventions have been studied for the treatment of delirium with few clearly proven to be of benefit. The most commonly cited agents for the treatment of delirium are antipsychotics—haloperidol and atypical antipsychotics. In contrast to the 2002 guidelines where haloperidol was recommended as the preferred agent for the treatment of ICU delirium [35], the present guideline's only statement on haloperidol is that there is no evidence that it decreases the length of delirium in adult ICU patients.

Recently, there has been a move towards the preferential use of atypical antipsychotics. In the treatment of schizophrenia, atypical antipsychotics have an improved safety profile compared to haloperidol [36], and this finding seems to hold true in ICU delirium literature as well [15, 37]. However, evidence of their efficacy in treating ICU delirium is mixed. In 2004, a prospective randomized trial compared haloperidol to olanzapine in 73 medical and surgical adult ICU patients with delirium screened by ICDSC and diagnosed by DSM-IV criteria. Both groups showed similar clinical improvement in delirium; however, there was no comparative placebo arm [38]. Notably, there were no side effects noted in the olanzapine group, whereas extrapyramidal symptoms were noted in six patients (13 %) in the haloperidol group [38]. The MIND trial published in 2010 compared haloperidol, ziprasidone and placebo in a double-blind, randomized-controlled trial in 101 mechanically ventilated adult medical and surgical ICU patients with delirium. There was no difference in the primary outcome of days alive without delirium or coma for the haloperidol, ziprasidone, and placebo groups, but given that this was a pilot trial designed to assess feasibility of a larger trial of this nature, the MIND trial may have been underpowered to properly examine this outcome [39]. Concurrently, a separate prospective, double-blind, randomized, placebo-controlled trial was published, examining quetiapine use in 36 adult medical and surgical ICU patients that were ICDSC positive for delirium. Quetiapine use was associated with shorter time to delirium resolution (1 vs. 4.5 days, $p = 0.001$) and reduced duration of delirium (36 vs. 120 h, $p = 0.006$) with no difference in the adverse effects of QTc prolongation and extrapyramidal symptoms [36]. It is based on this one trial that the 2013 ACCM guidelines state that atypical antipsychotics may reduce the duration of ICU delirium; however, they note that further study is needed to validate these results [7••].

As mentioned earlier, common antipsychotic side effects include extrapyramidal symptoms and QTc prolongation, and they should be avoided in patients with a prolonged QT interval or at risk for torsades de pointes [7••]. An additional consideration for the use of antipsychotics in the ICU is that these medications are often inappropriately continued well after ICU discharge. Kram et al. found that 84.2 % of patients receiving atypical antipsychotics for delirium had the drug continued after transfer from the ICU, and 28.6 % were given a prescription for the medication on discharge [40]. A study of elderly ICU survivors noted similar findings. Patients surviving ICU admission were often inappropriately discharged to home on atypical antipsychotics, 80 % of which were initiated in the ICU [41]. While these medications may be helpful in the treatment of delirium, they are not without risk of adverse reactions and evidence suggests that their use may inappropriately and inadvertently be continued well past ICU admission.

In addition to antipsychotics, dexmedetomidine, a potent and selective α-2 agonist, has shown promise as a sedative for the ICU population. As a drug with no γ-aminobutyric acid (GABA) and little anticholinergic activity that also induces a more natural sleep-like state [39], dexmedetomidine in theory seems to be positioned to have beneficial effects on delirium. Indeed, two double-blind, randomized trials have compared dexmedetomidine favorably to sedation with benzodiazepines. Compared to lorazepam as sedation in mechanically ventilated medical and surgical ICU patients, dexmedetomidine resulted in more days without delirium or coma (median days, 7.0 vs. 3.0; $p = 0.01$) and a decreased prevalence of coma (63 vs. 92 %; $p = 0.001$) [42]. When compared to midazolam in a similar population, sedation with dexmedetomidine resulted in a decreased prevalence of delirium (54 vs. 76.6 %, absolute difference 22.6 %; $p = 0.001$) as well as a decreased duration of mechanical ventilation [43]. These trials are the basis for the ACCM recommendation that dexmedetomidine be used for ICU patients with delirium (unrelated to alcohol or benzodiazepine withdrawal) preferentially over benzodiazepines [7••]. Data even exist suggesting faster resolution of hyperactive delirium when using dexmedetomidine compared to haloperidol [44]; however this study, conducted in 20 mechanically ventilated patients, needs to be validated in a larger, more rigorous fashion before firm conclusions can be made. The common side effects of dexmedetomidine are hypotension and bradycardia, most noticeable when using loading doses or high-maintenance doses [39].

Another class of medication investigated for treatment of delirium is cholinesterase inhibitors. Presently only approved for the palliative treatment of Alzheimer's disease, some studies have examined their use in delirium. Donepezil has been studied in two small double-blind, randomized-controlled trials for the prevention and treatment of delirium in non-ICU postoperative patients undergoing elective total joint replacement and hip fracture repair, respectively [45, 46]. Neither of these studies found any difference in delirium prevention or treatment, and one found a greater incidence of side effects in the donepezil group. A similarly negative result was found in a 2010 study examining rivastigmine for the treatment of ICU delirium. This double-blind, randomized, placebo-controlled study was halted only a quarter of the way through enrollment ($n = 104$) when the rivastigmine group showed increased mortality (22 vs. 8 %, $p = 0.07$) and duration of delirium (median 5 vs. 3 days, $p = 0.06$) compared to the placebo group [47]. While the trial was not completed, the evidence was strong enough for the ACCM to recommend against use of rivastigmine for delirium [7••].

Conclusion

As demonstrated by the wealth of research and the heterogeneity of the patients, ICU delirium, or acute brain dysfunction, is an important and complex problem with a real impact on patient outcomes, and its study is a rapidly growing field. While there are many risk factors for ICU delirium, the most significant are pre-existing dementia, history of hypertension, history of alcoholism, high severity of illness at admission as well as coma and benzodiazepine use [7••]. The CAM-ICU and the ICDSC are the recommended tools for diagnosis of ICU delirium [7••]. While many strategies have been studied for the prevention of ICU delirium, early mobility remains the only proven intervention [7••]. Care bundles such as the ABCDE bundle and various PAD bundles may also be potentially helpful in the prevention and treatment of ICU delirium, but they require further study. And although no medication has definitively shown efficacy in treating delirium, atypical antipsychotics and dexmedetomidine show the most promise [7••]. Care bundles, their individual components, and the various pharmacologic sedatives, sedation practices and protocols represent areas for future study in this field.

Compliance with Ethics Guidelines

Conflict of Interest Carolyn Heeder, Ruben J. Azocar, and Andrea Tsai declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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