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Intensive Care Unit Delirium

A Review of Diagnosis, Prevention, and Treatment

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A 77-YR-OLD man is admitted to the hospital after sustaining a hip fracture. He has a medical history of chronic obstructive pulmonary disease, hypertension, hyperlipidemia, chronic back pain, and hearing loss. Before surgery, he receives midazolam for agitation and morphine for pain control. He undergoes a general anesthetic for his fracture repair, requiring high doses of fentanyl for pain control. Postoperatively, he has poor pulmonary mechanics and is taken to the intensive care unit (ICU) intubated and mechanically ventilated. On postoperative day 1, his sedation is weaned and he is put on a spontaneous breathing trial. While he appears intermittently awake, he will not follow commands and only intermittently makes eye contact. The patient is left intubated due to his altered mental status.

Delirium is a common problem in critically ill patients but has only recently been recognized as a serious entity associated with important clinical outcomes, including increased days on mechanical ventilation, length of hospital stay, cost of care, long-term cognitive impairment, requirement for postdischarge institutionalization, and mortality.[1–3] Validated delirium screening tools for ICU patients, which can be used by a wide range of personnel, have improved diagnosis, and routine delirium assessment is now recommended as the standard of care in the ICU. Furthermore, potential pharmacologic (*e.g.*, antipsychotics and dexmedetomidine) and nonpharmacologic (*e.g.*, early physical therapy and sleep hygiene) prevention and treatment strategies have been studied to reduce delirium and improve its associated outcomes with varying results. This review will explore the risk factors for ICU delirium, tools for its diagnosis, preventative strategies, and its potential treatments. This information can be utilized throughout the patient's hospitalization, including in the perioperative environment, and can be practiced by anesthesiologists and intensivists to improve patient care.

Characterizing Delirium

The term "delirium" is frequently used across clinical settings to describe patients with altered mental status, but its proper diagnosis requires specific manifestations to be present. Delirium is defined in *The Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition* (DSM-5)[4] as a reduced ability to direct, focus, sustain, and shift attention. This is coupled with a change in cognition, in the form of memory deficit, disorientation, or perceptual disturbances. Importantly, the inattention and change in cognition cannot be accounted for by a baseline neurocognitive disorder (*e.g.*, dementia) or a severely reduced level of arousal (*e.g.*, sedative administration and coma). The disturbance in mental status must be an acute change from baseline and fluctuate throughout the day but may occur in addition to baseline disease (*e.g.*, delirium superimposed on dementia and delirium after stroke). Delirium diagnosis identifies the constellation of altered brain function signs but does not identify the etiology. It should, therefore, prompt further investigation into potential patient vulnerability factors and precipitating factors associated with the current illness or hospital course.

Incidence

The incidence of delirium varies widely depending on the patient population examined and the method of diagnosis (*e.g.*, psychiatric evaluation *vs.* nurse screening tool). It has been reported to occur in 16 to 89% of hospitalized patients,

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including up to 45% of postanesthesia care unit patients and 50% of postoperative patients on the ward.[5,6] The incidence, however, seems to be the highest in the ICU, with up to 80% of mechanically ventilated patients having delirium.[7,8] Delirium can present with three motor subtypes—hyperactive, hypoactive, and mixed—that may carry different prognoses.[9,10] The two most common types of delirium, as studied in a medical ICU, were mixed at 54.9% and hypoactive at 43.5% of delirious patients.[11] Hypoactive delirium is characterized by slowed mentation, lethargy, and decreased movement. It is found more commonly in the elderly, with age more than 65 yr being an independent risk factor.[11] It typically requires active screening with delirium assessment tools to diagnose since it is often less clinically apparent than the restlessness and agitated behavior of hyperactive delirium. In a study of patients admitted to the ICU postoperatively after elective procedures, patients who suffered from hypoactive delirium had increased 6-month mortality compared to the patients who suffered from other subtypes of delirium (32.0 *vs.* 8.7%; $P = 0.04$).[12]

Risk Factors

Known risk factors for developing delirium are numerous and commonly separated into factors that predispose a patient to delirium and other factors that precipitate the development of delirium (table 1). Advanced age and baseline cognitive impairment have been consistently found to increase delirium risk across a variety of hospital settings.[5] Similarly, patients with increased comorbid disease burden (especially respiratory disease)[13] and frailty[14] appear to be at higher risk. Thus, patients with lower cognitive and physical reserve likely possess decreased capacity to maintain normal brain functioning in response to stress (*e.g.*, surgery and critical illness) and are, therefore, at higher risk for delirium.[15,16] Similarly, a more significant systemic insult, such as sepsis, prolonged mechanical ventilation, or major surgery (in particular complex abdominal, hip fracture, and cardiac surgery), will increase the risk of delirium compared to a lesser physiologic insult.[5] Increased pain levels have repeatedly been shown to increase delirium, especially in the postoperative setting, potentially due to heightened stress response and altered neurotransmission.[17,18]

Several medications have been associated with delirium. With regard to sedative and analgesic medications, use of lorazepam, midazolam, meperidine, and morphine is most strongly associated with a higher risk of delirium, likely due to their longer duration of actions and increased risk of drug accumulation with altered organ function (*e.g.*, renal and hepatic insufficiency), compared to agents such as propofol, dexmedetomidine, and fentanyl.[5,13] Sedation with benzodiazepine infusions for mechanical ventilation, in particular, carries a higher risk of delirium compared to other sedative regimens,[19–21] as does deep levels of sedation when compared to light sedation.[19] Additionally, medications with anticholinergic properties (*e.g.*, diphenhydramine, promethazine, and cyclobenzaprine) can precipitate delirium, potentially through altered neurotransmission or reduced neuronal control of inflammation.[22,23] Steroid administration during critical illness, either as a marker of shock severity or due to their known psychologic side effects, has been associated with transition to delirium.[24] Dopamine is a neurotransmitter, and medications that potentiate its effects can cause psychosis whereas those that block its effects are used as antipsychotics. Dopamine administration for shock greatly increases the odds of requiring treatment for delirium after adjustment for severity of illness factors although direct comparison to other vasoactive medications was not performed.[25]

Identifying Delirium in the ICU Setting

The definitive standard for delirium diagnosis is evaluation by a psychiatrist using DSM-5 criteria, which is not feasible on a routine basis. A number of screening tools, therefore, have been developed and validated for clinical use by a wide range of personnel. Importantly, it has been demonstrated that most delirium in the ICU goes undiagnosed without using a regular screening tool,[26] and current guidelines recommend the routine screening for delirium in all ICU patients.[27] Importantly, a patient must be arousable to voice to assess for delirium. Thus, an arousal/sedation tool such as the Richmond Agitation-Sedation Scale (RASS)[28] must be utilized along with a delirium assessment tool. There are seven validated instruments to assess delirium in critically ill patients (table 2).[7,29] Of these, the Confusion Assessment Method for the Intensive Care Unit (CAM-ICU)[8] and the Intensive Care Delirium Screening Checklist (ICDSC)[30] are the most widely studied. Additionally, based on the assessment of psychometric properties, the CAM-ICU and

Table 1. Delirium Risk Factors

Predisposing Factors	Precipitating Factors	
Advanced age	Metabolic disturbances	Benzodiazepines
Baseline cognitive impairment	Hypotension	Opioids (meperidine and morphine)
Increased comorbid disease	Sepsis	Deep *vs.* light sedation
Frailty	Poor pain control	Anticholinergics
Alcohol and drug abuse	Mechanical ventilation	Steroids
High severity of illness	Sleep disturbances	Surgery (abdominal, cardiac, and hip)

Risk factors for delirium are numerous and can be separated into predisposing patient factors and precipitating clinical factors.

Table 2. Validated Instruments to Assess Delirium in Critically Ill Patients

				Initial ICU Validation			
Instrument	Features Assessed	Time Period	Scoring	Assessor	Comparator	n	Results
Confusion Assessment Method for the ICU	Acute changes or fluctuation in mental status, inattention, disorganized thinking, altered level of consciousness	Short moment in time assessment	Positive or negative	Research nurses	Psychiatric expert assessment with DSM-IV criteria	111	100 and 93% sensitivities, 98 and 100% specificities
Intensive Care Delirium Screening Checklist	Altered level of consciousness, inattention, disorientation, psychosis, altered psychomotor activity, inappropriate speech/mood, sleep disturbance, and symptom fluctuation	Assessment over nursing shift or day	0–8	Research team members completed checklist for 24-h periods	Psychiatric expert assessment with DSM-IV criteria	93	99% sensitivity and 64% specificity if ≥ 4 features
Cognitive Test for Delirium	Orientation, attention span, memory, comprehension and conceptual reasoning, and vigilance	Longer moment in time assessment	0–30	Psychologist technician	Psychiatric expert assessment with DSM-IIIR criteria	103	100% sensitivity and 95% specificity if score ≤ 18*
Abbreviated Cognitive Test for Delirium	Visual attention span, recognition memory	Short moment in time assessment	0–24	Psychologist technician	Psychiatric expert assessment with DSM-IIIR criteria	100	95% sensitivity and 99% specificity if score ≤ 10*
Delirium Detection Score	Agitation, anxiety, hallucination, orientation, seizures, tremor, paroxysmal sweating, altered sleep-wake rhythm	Longer moment in time assessment	0–56	Clinical physicians and nurses	Sedation-Agitation Scale and defined clinical assessment	1,073	69% sensitivity and 75% specificity if score ≥ 8
Neelon and Champagne Confusion Scale	Attention, command, orientation, appearance, motor, verbal, vital function, oxygen saturation, urinary continence	Short moment in time assessment	0–30	Clinical nurses	Psychiatric intern assessment with DSM-IV criteria	105	97% sensitivity and 83% specificity if score ≤ 24
Nursing Delirium Screening Scale	Disorientation, inappropriate behavior, inappropriate communication, hallucination, psychomotor retardation	Assessment over nursing shift or moment in time assessment	0–10	Research physicians and nurses	Psychiatric expert assessment with DSM-IV criteria	156	82% sensitivity and 83% specificity if score ≥ 2

Seven instruments have been validated to assess for delirium in critically ill patients. These instruments vary in the features assessed, time of assessment, scoring scale, and validation. The Society of Critical Care Medicine's Pain, Agitation, and Delirium guidelines recommend the Confusion Assessment Method for the Intensive Care Unit (ICU) or Intensive Care Delirium Screening Checklist for routine monitoring of delirium in the ICU.

*Assessed delirium *versus* dementia, depression, and schizophrenia and not delirium *versus* normal mental status or coma.

DSM = Diagnostic and Statistical Manual of Mental Disorders.

ICDSC are the recommended instruments by the Society of Critical Care Medicine's Pain, Agitation, and Delirium guidelines for monitoring delirium in ICU patients.[27]

The CAM-ICU is an abbreviated version of the Confusion Assessment Method[31] designed to fit the needs of nonverbal and verbal ICU patients. Originally described by Ely *et al.*[8] in 2001, the CAM-ICU tool assesses the same four cardinal features as the Confusion Assessment Method—acute changes/fluctuations in mental status, inattention, disorganized thinking, and an altered level of consciousness—but in a condensed manner ideal for the ICU setting. To validate the CAM-ICU, assessments were performed in

111 patients (471 total evaluations) by two independent nurses and compared to expert psychiatric assessment using the DSM-IV criteria. The study found sensitivities of 100 and 93% and specificities of 98 and 100%, respectively.[8] The moment in time delirium assessment with the CAM-ICU requires less than 2 min to complete, which has prompted its use in hospital settings outside the ICU. While the majority of subsequent studies have shown high sensitivity and specificity for the CAM-ICU across a variety of patients (*e.g.*, medical and surgical) and severities of illness,[29,32,33] some studies have found lower sensitivity of the CAM-ICU when used in less severely ill patients outside of the ICU, such as the postanesthesia care unit (although these studies have shown specificity near or above 90%).[34] A recent systematic review of studies in ICU patients demonstrated pooled sensitivity of 80% and specificity of 96% for the CAM-ICU.[35] The ICDSC assesses eight diagnostic features of delirium over an entire nursing shift (altered level of consciousness, inattention, disorientation, psychosis, altered psychomotor activity, inappropriate speech/mood, sleep disturbance, and symptom fluctuation).[30] In its validation, the ICDSC was performed in 93 patients and compared to psychiatric evaluation. The presence of four or more of the listed features had 99% sensitivity and 64% specificity for delirium.[30] A recent systematic review of studies in ICU patients demonstrated pooled sensitivity of 74% and specificity of 82% for the ICDSC.[35]

Delirium assessment tools such as the CAM-ICU and ICDSC should not be viewed solely as tools for research but rather as pivotal components in the care of patients. Current clinical guidelines recommend using either the CAM-ICU or ICDSC for routine delirium assessment in the critically ill.[27] These assessments can be effectively performed outside of the research setting by clinical nursing staff if appropriate education and training is provided (resources available online).[36] Successful implementation of routine delirium screening in the ICU requires institutional acknowledgment of the necessity for delirium screening, physician and nurse leaders to serve as delirium experts and resources, didactic instruction, case-based scenarios, bedside demonstrations, adjustment of techniques to fit patient population (*e.g.*, language, questions, and visuals used during assessment), follow-up teaching, and routine presentation of results on interdisciplinary rounds (*e.g.*, the Brain Roadmap).[37] Large-scale implementation trials have shown that nurses can use the CAM-ICU routinely with high levels of compliance and reliability[38,39] and that compliance and reliability of measurements at the bedside can be sustained multiple years after implementation.[40] Given the fluctuating course of delirium, it is important that these assessments are performed in a serial nature (for an assessment at any given point in time may not capture complete symptomatology) and combined with chart review and discussion with family and caregivers.

Delirium Prevention

A large portion of ICU patients develop delirium, especially those who are mechanically ventilated or who have other risk factors on admission. While many of these risk factors are often nonmodifiable by clinicians, several preventative

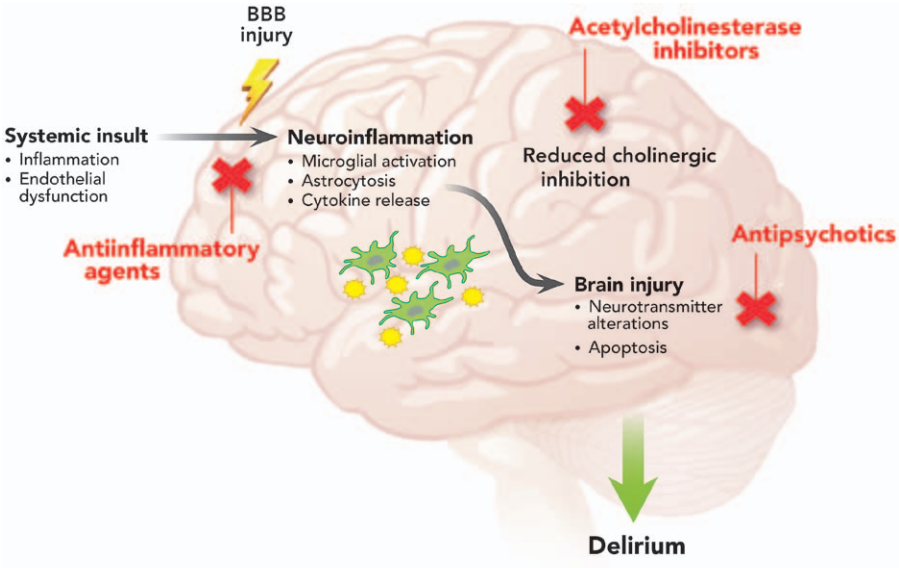

Fig. 1. Potential mechanisms and therapies for intensive care unit (ICU) delirium. Hypothesized mechanisms for ICU delirium include systemic inflammation, endothelial dysfunction, increased blood–brain barrier (BBB) permeability, and reduced cholinergic control of the inflammatory response that, along with baseline patient vulnerability factors, predispose patients to neuroinflammation and subsequent neuronal injury. Primed and overactivated microglia from these processes may also exacerbate the pathophysiologic changes. Therapeutic agents studied for the prevention or treatment of ICU delirium have targeted these pathways.

strategies have been demonstrated to reduce the incidence of ICU delirium.

Pharmacologic Prophylaxis

Multiple pathophysiologic processes likely contribute to delirium, and a number of pharmacologic prophylaxis agents have subsequently been studied to decrease delirium incidence (fig. 1).[41,42] This includes agents to reduce dopamine activity and improve neurotransmitter imbalances (*e.g.*, antipsychotics) and agents that increase cholinergic activity as low cholinergic activity and anticholinergic medications have been linked to delirium (*e.g.*, acetylcholinesterase inhibitors). The majority of recent animal and human research studies have focused on systemic insults (*e.g.*, surgery and sepsis) leading to inflammatory signaling through the blood–brain barrier, resulting in neuroinflammation and neuronal injury.[43–48] Thus, agents to reduce systemic inflammation and decrease the neuroinflammatory cascade (*e.g.*, steroids and statins) are also being examined.

Studies investigating whether prophylactic antipsychotic administration reduces the incidence or duration of delirium have had mixed results. Perioperative haloperidol (1.5 mg/day) prophylaxis in elderly hip surgery patients did not affect the incidence of delirium but did decrease the duration (5.4 *vs.* 11.8 days; $P < 0.001$) compared to placebo.[49] A low-dose haloperidol bolus (0.5 mg intravenously) followed by an infusion (0.1 mg/h for 12 hr) in elderly patients admitted to the ICU after noncardiac surgery decreased the incidence of delirium only after intraabdominal surgeries (14.5 *vs.* 24.7%; $P = 0.018$).[50] A before–after study of intravenous haloperidol (1 mg every 8 h) as prophylaxis in ICU patients deemed high risk for delirium showed significantly less incidence ($P = 0.01$) and duration ($P = 0.003$) of delirium.[51] A more recent randomized controlled trial—The Haloperidol Effectiveness in Intensive Care Unit Delirium (HOPE-ICU) study—however, showed no difference in days alive and free of delirium or coma between patients prophylactically treated with intravenous haloperidol (2.5 mg every 8 h) and those treated with placebo.[52] Oversedation was the most common adverse event in the trial (15% in the haloperidol group); those treated with haloperidol, however, were less likely to develop agitation with an RASS score greater than or equal to +2 (13 *vs.* 20%; $P = 0.0075$).

Numerous studies have examined agents to prevent delirium after cardiac surgery. In a blinded, placebo-controlled trial of 126 patients undergoing elective cardiac surgery with cardiopulmonary bypass, a single dose of sublingual risperidone (1 mg) upon regaining consciousness reduced the incidence of delirium compared to that of placebo (11 *vs.* 32%; $P = 0.009$).[53] Another study of risperidone in elderly patients requiring cardiac surgery with cardiopulmonary bypass examined whether repeated doses (0.5 mg every 12 h) could prevent the development of delirium in patients exhibiting signs of acute brain dysfunction but who did not yet meet delirium criteria (referred to as subsyndromal delirium).[54] They found a lower incidence of delirium development in the risperidone group compared to the placebo group (13.7 *vs.* 34%; $P = 0.031$). These studies utilized validated delirium assessments, and the incidence of delirium in the placebo groups was similar to that in other published cohorts.[55] The positive results seen with risperidone need to be confirmed in additional larger cohorts before routine administration can be recommended. Prophylactic administration of dexamethasone upon induction of anesthesia to reduce the subsequent systemic and neurologic inflammatory cascade of surgery and cardiopulmonary bypass did not reduce the incidence or duration of delirium in the first 4 days after surgery compared to placebo in a study of patients undergoing cardiac surgery with cardiopulmonary bypass.[56] Gamberini *et al.*[57] performed a randomized controlled trial of a 7-day course of the acetylcholinesterase inhibitor rivastigmine *versus* placebo in patients undergoing elective cardiac surgery with cardiopulmonary bypass but found no difference in the incidence of postoperative delirium.

Donepezil, an acetylcholinesterase inhibitor used commonly in dementia patients, has been studied with regard to delirium prophylaxis but with negative results. In a study of 80 elderly patients undergoing elective total joint replacement surgery, patients were randomized to donepezil or placebo for 14 days before surgery and 14 days afterward.[58] No significant difference in delirium incidence was found between the groups. Similar results were seen in a pilot trial of 16 elderly patients undergoing hip fracture repair randomized to donepezil or placebo within 24 h of surgery.[59] The donepezil treatment group experienced more adverse effects and had no significant improvements in delirium presence or severity. A randomized, double-blind, placebo-controlled trial of 33 patients undergoing elective total hip replacement also found no significant difference in the incidence of delirium.[60]

There is interest in the pleiotropic antiinflammatory effects of statin medications with regard to delirium.[61] Ongoing statin therapy while in the ICU has been shown to be associated with lower overall risk of delirium in two studies,[62,63] and increasing duration of statin withholding in chronic statin users increases the odds of developing delirium.[63] Further randomized controlled trials are needed to provide evidence of the ability of statins to prevent delirium.

Despite the multiple agents evaluated covering a variety of pathophysiologic pathways, there remains a lack of proven prophylactic agents to reduce delirium. In addition, many of these agents have significant side effects, in particular the antipsychotics, which may prolong the QT interval, lead to oversedation, or cause neuroleptic malignant syndrome. This emphasizes the necessity of nonpharmacologic preventative measures to improve delirium outcomes.

Choice of Sedation for Mechanical Ventilation

The type of sedation used in mechanically ventilated patients in the ICU can affect rates of delirium. Currently,

it is recommended by the Pain, Agitation, and Delirium guidelines to perform analgesia-first sedation followed by nonbenzodiazepine medications if needed for sedation in mechanically ventilated patients in the ICU.[27] This is partly based upon evidence demonstrating increased risk of delirium with traditional sedation regimens involving continuous benzodiazepine infusions and deeper levels of sedation. Pandharipande *et al.*[19] compared sedation with dexmedetomidine *versus* lorazepam infusion in intubated patients, assessing rates of delirium (as defined by CAM-ICU), coma, ICU length of stay, and mortality. This study of 106 critically ill patients found that the patients receiving dexmedetomidine had more delirium/coma-free days than those receiving lorazepam (7 *vs.* 3; $P = 0.01$) and less coma (63 *vs.* 92%; $P < 0.001$). There was no difference in antipsychotic use between the groups. These findings were subsequently confirmed with a multicenter trial by Riker *et al.*,[20] in which dexmedetomidine was compared to midazolam for targeted sedation. They found similar results, with 54% of the dexmedetomidine-treated patients developing delirium, while 76.6% of the midazolam-treated patients developed delirium ($P \leq 0.001$).[20] In comparing sedation with propofol *versus* dexmedetomidine, a study found fewer neurocognitive disorders and improved arousal, cooperation, and communication with dexmedetomidine.[64] However, they only assessed the CAM-ICU once, 48 h after the infusions had been discontinued, and found no difference in delirium. A recent Cochrane metaanalysis pooled seven randomized controlled trials comparing sedation with dexmedetomidine to sedation with benzodiazepines, propofol, or "standard care" that included propofol or midazolam.[65] The risk of delirium was numerically lower with dexmedetomidine but not statistically significant (risk ratio [RR], 0.85; 95% CI, 0.63 to 1.14). Subgroup analyses showed that the risk of delirium was lower in patients receiving dexmedetomidine than in those receiving benzodiazepines (RR, 0.81; 95% CI, 0.59 to 1.09; 1,007 participants) or propofol (RR, 0.37; 95% CI, 0.16 to 0.87; 495 participants).[65] Overall, the authors found high rates of heterogeneity between the studies, including the baseline risk for delirium, time in ICU before enrollment and assessment, frequency and duration of delirium assessments, and levels of sedation targeted, all of which would bias delirium outcomes. They recommended that further studies stratify randomized patients based on delirium risk. Dexmedetomidine has additionally been found to reduce delirium rates when used after cardiac surgery.[66] Most recently, a randomized controlled trial of dexmedetomidine *versus* propofol for ICU sedation in 183 patients after cardiac surgery found a decreased incidence (17.5 *vs.* 31.5%; $P = 0.028$) and reduced duration of delirium (2 *vs.* 3 days; $P = 0.04$) in the dexmedetomidine group, leading to a reduction in ICU time and cost related to delirium.[67]

In the sedation studies outlined, analgesia (and likely supplemental sedation) was provided with fentanyl in addition to the sedative medications administered. Similar fentanyl requirements were found between dexmedetomidine, midazolam, and propofol regimens[20,64] with the exception of after cardiac surgery, in which dexmedetomidine patients required less analgesic medications.[67] There are now data examining analgesia-based sedation regimens and their effect on delirium. One trial showed that patients treated only with intermittent morphine had higher rates of agitated delirium (20 *vs.* 7%; $P = 0.04$) compared to patients sedated with propofol or midazolam (hypoactive delirium was not assessed in this study) although patients receiving analgosedation had shorter ICU lengths of stay.[68] When comparing morphine to dexmedetomidine for sedation after cardiac surgery, patients receiving a morphine-based regimen had similar overall incidence of delirium but had an increased duration of delirium by 3 days ($P = 0.03$).[69]

Exposure to sedative medications and deeper levels of sedation are associated with increased risk of delirium, but questions have arisen regarding whether delirium that abates quickly after sedative discontinuation—rapidly reversible, sedation-related delirium—portends similar outcomes to delirium that persists after sedative discontinuation—persistent delirium. A prospective cohort study performed delirium assessments before and after sedative discontinuation.[70] It found delirium to be extremely prevalent, with 89% of patients developing delirium, but only a small group of patients (12%) had delirium that abated after sedation interruption (rapidly reversible, sedation-related delirium).[70] This group with rapidly reversible, sedation-related delirium had fewer ventilator days ($P < 0.001$), ICU days ($P = 0.001$), and hospital days ($P < 0.001$), was more likely to be discharged home *versus* an institution ($P < 0.001$), and had higher survival rates ($P < 0.001$) than those whose delirium persisted. Persistent delirium (77% of the cohort) remained associated with worse outcomes. This study has important clinical implications: (1) recent sedative administration should be carefully considered when evaluating for delirium; (2) the effect of persistent delirium on negative outcomes is likely greater than measured in previous studies as those with rapidly reversible, sedation-related delirium were included, biasing those studies toward the null, and (3) only a small subset of patients on sedative medications resolve their delirium rapidly after discontinuation of those medications, underlining the importance of monitoring for delirium even in patients on sedative medications.

Early Mobility

Early physical and occupational therapy in intubated and mechanically ventilated patients coordinated among nursing staff, physical therapists, and respiratory therapists is feasible, safe, and has been demonstrated to reduce ICU delirium.[71] Therapy can progress from passive range of motion to active range of motion, exercise in bed, sitting, standing, walking, and activity of daily living training depending on a patient's sedation level and physical abilities. Schweickert *et al.*[71] conducted a multicenter, randomized controlled trial of

104 hemodynamically stable medical ICU patients to look at the effect of daily sedation interruptions paired with physical and occupational therapy on long-term functional independence, with secondary outcomes that included delirium. After patients were randomized, those in the intervention group had regular sessions with the physical and occupational therapists while their sedation was paused, progressing from range-of-motion exercises to walking. They found a median of 2 days of ICU delirium in the early physical therapy group, whereas the control group had a median of 4 days of delirium (P = 0.03). Both groups had similar sedation and analgesia although the physical therapy group had, on average, more time without sedation than the control group.

Sleep Hygiene

Fragmented sleep has been associated with delirium, and studies have evaluated ways to improve sleep hygiene (*i.e.*, habits and practices conducive to sleep) by providing more favorable environments for sleep in the ICU. Providing ear plugs to patients in the ICU has been shown to reduce the incidence of delirium and improve sleep perception.[72] A quality improvement project aimed at improving sleep by minimizing sleep disruptions, promoting normal circadian rhythms, using nonpharmacologic sleep aids, and implementing alternative sleep medications when necessary (*e.g.*, zolpidem, haloperidol, and atypical antipsychotics) has also been shown to decrease the incidence of ICU delirium/coma and improve daily delirium/coma-free status although without improved perceived sleep quality.[73] The authors subsequently found no association between daily perceived sleep quality rating and transition to delirium.[21] These studies suggest that maintaining practices conducive to sleep is important to prevent delirium in the ICU but highlight the difficulty in monitoring sleep and differentiating between sleep perception and measures of actual sleep.

While outwardly appearing to improve sleep, sedative administration in the ICU has been shown to differentially alter sleep patterns when measured by polysomnography. In a study of 12 ICU patients not requiring vasoactive or sedative medications, patients were monitored with polysomnography for two nights, one of which they received propofol and the other no sedation to serve as a control.[74] They found that propofol administration significantly decreased the number of patients exhibiting rapid eye movement (REM) sleep (P = 0.02) and the percentage of REM sleep (P = 0.04). In a similar study of 13 hemodynamically stable ICU patients not requiring vasoactive or sedative medications, patients were monitored with polysomnography for three nights, receiving dexmedetomidine on the second night only and no sedatives the other two nights to serve as a control.[75] They found that dexmedetomidine improved sleep efficiency (P < 0.002) and stage 2 sleep (P = 0.006) while decreasing nighttime sleep fragmentation (P = 0.023). These limited data in critically ill patients are consistent with additional data indicating that sedation with dexmedetomidine more closely resembles natural non-REM sleep than sedation with γ-aminobutyric acid–mediated agents.[76] However, clinical studies investigating the interactions between sedative agents, sleep patterns, and delirium have not yet been performed.

Interest in sleep disturbances in delirium has led to studies investigating the role of melatonin in delirium. Abnormal release of circadian melatonin has been found in septic ICU patients,[77] and melatonin levels have been found to be significantly lower in postoperative ICU patients with delirium than in those without delirium.[78] Importantly, data regarding whether melatonin or melatonin agonists improve sleep quality and circadian rhythms in ICU patients are limited and unclear. In a randomized controlled trial of 24 patients on mechanical ventilation after tracheostomy, melatonin supplementation increased nocturnal sleep efficiency as measured by the bispectral index but not by other sleep measurements.[79] Another study of 32 patients with tracheostomy found no significant difference in sleep duration as measured by nursing assessment.[80]

One of the first randomized controlled trials examining melatonin as an agent for delirium prevention found that melatonin (0.5 mg nightly) was associated with a lower risk of delirium compared to placebo (12.0 *vs.* 31.0%; P = 0.014) in 145 elderly patients admitted to a medical acute care unit.[81] A double-blind, randomized controlled trial of melatonin (3 mg nightly) *versus* placebo in 378 patients with hip fracture, however, did not demonstrate a difference in the incidence of delirium.[82] Ramelteon, a melatonin receptor agonist, has been shown to lower risk of delirium (3 *vs.* 32%; P = 0.003) in a randomized controlled trial of 67 elderly patients admitted to a medical ICU or acute care ward who received ramelteon (8 mg nightly) or placebo.[83] They did not find any benefit of ramelteon on sleep metrics, making it unclear whether the effects of ramelteon on delirium are related to sleep. Limitations of studies examining melatonin and ramelteon include the lack of sleep measurement *via* polysomnography or electroencephalogram and inability to adjust for actual sleep differences between groups. While generally well tolerated, these agents are not benign and may cause headache, daytime sleepiness, dizziness, and depressive symptoms. Thus, large, randomized controlled trials with direct sleep measurement are required to clarify the role of pharmacologic agents in sleep and delirium prevention in the ICU before prophylactic administration can be recommended. A recent systemic review concluded that nonpharmacologic and pharmacologic sleep interventions may be a promising approach to improve delirium but that current research is limited by varied methodologies and significant bias, requiring a systematic approach in future research to evaluate the complex interactions between sleep interventions and delirium.[84]

Sedation Bundles

While several studies have identified specific interventions that reduce delirium rates, others have combined the evidence-based prevention techniques into bundles to evaluate if, when applied together in a consistent manner, they could reduce delirium rates even further. The Awakening and Breathing Coordination, Delirium Monitoring/Management, and Early Exercise/Mobility (ABCDE) bundle was originally published in 2011[85] and studied in a before–after trial between 2010 and 2012 at a tertiary medical center.[86] Critically ill patients were enrolled from five separate ICUs, one step down unit, and a hematology/oncology specialty unit. The patients in the "before" group were treated as per the standard practice, which included spontaneous awakening trials (SAT) and spontaneous breathing trials (SBT) but no consistent delirium screening by clinical providers. In the "after" group, the ABCDE bundle was implemented and included a daily SAT, which was then coordinated with an SBT, scheduled RASS and CAM-ICU assessments, delirium action plan discussions among providers, and early mobility evaluations and performance. Patients in the postimplementation bundle group had less delirium (48.7 *vs.* 62.3%; $P = 0.02$) and a lower percent of ICU days spent delirious (33 *vs.* 50%; $P = 0.002$). There was a significant independent effect of the ABCDE bundle on decreasing delirium ($P = 0.03$).

Similar to the ABCDE bundle, another study examined a quality improvement project aimed at reducing benzodiazepine exposure, lightening sedation, and increasing mobility. This study found a significant increase in the days alive without delirium (53 *vs.* 21%; $P = 0.003$).[87] In a before–after study of protocolized deescalation of sedation and required RASS and CAM-ICU assessments, the authors found a significant reduction in the odds of developing delirium (odds ratio, 0.67; $P = 0.01$) along with a reduction in mechanical ventilation duration ($P = 0.04$) and hospital length of stay ($P = 0.02$).[88] Thus, current evidence supports the use of sedation bundles to decrease the development of delirium.

The American Association of Critical Care Nurses has developed a toolkit for implementing the ABCDE bundle at the bedside.[89] This toolkit includes resources for the specific components of the bundle and tools for overall

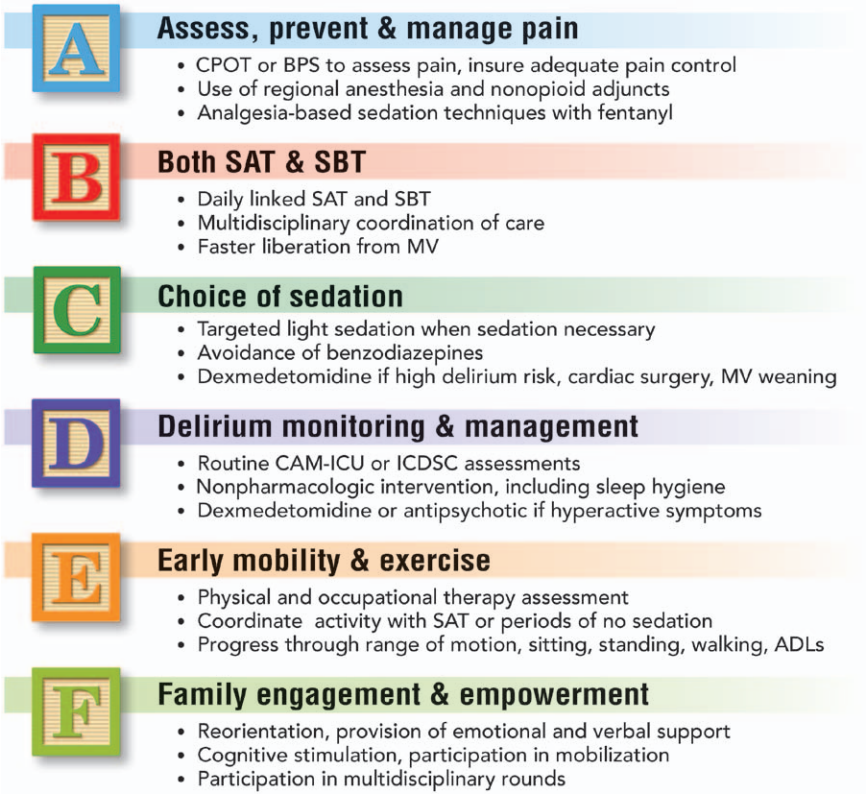

Fig. 2. The ABCDEF (*A*ssessment and management of Pain, *B*oth SATs and SBTs, *C*hoice of sedation if required, *D*elirium monitoring and management, *E*arly mobility and exercise, and *F*amily engagement and empowerment) building blocks of intensive care unit (ICU) delirium management. Multidisciplinary ICU care bundles focusing on pain management, liberation from mechanical ventilation, light sedation or no sedation, avoidance of benzodiazepines, routine delirium monitoring, and early mobility have been shown to reduce delirium and improve patient outcomes. More information on the ABCDEF bundle can be found online.[36,90] ADLs = activities of daily living; BPS = Behavioral Pain Scale; CAM-ICU = Confusion Assessment Method for the Intensive Care Unit; CPOT = Critical-Care Pain Observation Tool; ICDSC = Intensive Care Delirium Screening Checklist; MV = mechanical ventilation; SAT = spontaneous awakening trial; SBT = spontaneous breathing trial.

implementation. The Society of Critical Care Medicine has recently launched the ICU Liberation collaborative with a reworking of the ABCDE bundle.[90] The now coined "ABCDEF" bundle involves *A*ssessment and management of Pain, *B*oth SATs and SBTs, *C*hoice of sedation if required, *D*elirium monitoring and management, *E*arly mobility and exercise, and *F*amily engagement and empowerment (fig. 2).

Delirium Treatment

Prevention of delirium is of utmost importance because the number of evidence-based pharmacologic treatment options is minimal, and those that exist have significant limitations. Therefore, the cornerstone of delirium treatment is correction of the patient's medical conditions that may be contributing to delirium.

Potential Treatment Options

Despite the abundance of literature and research on delirium, there remains a paucity of large, randomized controlled trials of pharmacologic treatments for delirium. The clinical approach to pharmacologic treatment often includes the use of typical (*e.g.*, haloperidol) and atypical (*e.g.*, olanzapine, quetiapine, and ziprasidone) antipsychotics, but evidence on their efficacy is limited and conflicting. In a pilot study of 101 ICU patients at risk for delirium, placebo *versus* haloperidol (5 mg) *versus* ziprasidone (40 mg) in repeated doses showed no difference in delirium-free days among all three groups.[91] Another evaluation of haloperidol (2.5 to 5 mg every 8 h) *versus* olanzapine (5 mg daily) showed no difference in length of delirium in 73 ICU patients although the patients receiving haloperidol did have more extrapyramidal side effects.[92] In a study of 36 ICU patients with delirium requiring intravenous haloperidol, patients were randomized to scheduled quetiapine (50 mg every 12 h) or placebo in addition to the "as-needed" haloperidol. The group that received quetiapine had a faster resolution of the first episode of delirium (36 *vs.* 120 h; $P = 0.006$) although mortality and ICU length of stay were similar.[93] Based on evidence that impaired cholinergic neurotransmission may lead to the development of delirium, rivastigmine (1.5 to 6 mg every 12 h) was studied as an adjunct to haloperidol *versus* a combination of placebo and haloperidol.[94] This study found no decrease in the duration of delirium, and there was a trend toward increased mortality in the rivastigmine group.[94]

In a small pilot study of patients with agitated delirium preventing tracheal extubation, 20 patients were randomized to a dexmedetomidine (0.2 to 0.7 μg kg^{-1} h^{-1}) or haloperidol (0.5 to 2 mg/h) infusion. The patients receiving dexmedetomidine had a shorter time to extubation (19.9 *vs.* 42.5 h; $P = 0.016$), ICU length of stay (1.5 *vs.* 6.5 days; $P = 0.004$), and less requirement for tracheostomy.[95] The recently published Dexmedetomidine to Lessen ICU Agitation (DahLIA) trial randomized patients whose critical illness had otherwise resolved, but for whom weaning from mechanical ventilation was hampered by hyperactive or agitated delirium, to receive up to 7 days of intravenous dexmedetomidine up to 1.5 μg kg^{-1} h^{-1} (n = 41) or placebo (n = 33).[96] Patients treated with dexmedetomidine had increased ventilator-free time at 7 days (144.8 *vs.* 127.5 h; $P = 0.01$) and had faster resolution of their delirium symptoms (23.3 *vs.* 40.0 h; $P = 0.01$). No difference was found in bradycardia requiring interruption of study drug or hypotension requiring vasopressor support between groups. A recently published, nonrandomized study examined the effectiveness of dexmedetomidine as a rescue therapy for nonintubated ICU patients with hyperactive delirium.[97] Patients whose agitated delirium failed to be controlled with up to 30 mg intravenous haloperidol (n = 46) received dexmedetomidine (0.2 to 0.7 μg kg^{-1} h^{-1}). Patients whose agitated delirium improved after haloperidol (n = 86) received a haloperidol infusion (0.5 to 1 mg/h). Patients receiving dexmedetomidine had a higher percentage of time at target sedation (92 *vs.* 59%; $P = 0.001$), less oversedation (0 *vs.* 11.6%; $P = 0.01$), and a shorter ICU length of stay (3.1 *vs.* 6.4; $P < 0.001$) without increased incidence of hemodynamic side effects.[97] Additionally, the overall failure rate for haloperidol in this study was 43% when including patients with delirium refractory to haloperidol and those in whom haloperidol administration resulted in adverse events, demonstrating the limited efficacy of antipsychotic agents in the treatment of ICU delirium.

Treatment Algorithms

Overall, the evidence does not support a single effective pharmacologic approach to the treatment of delirium in the ICU. The treatment options available also have significant side effects. Antipsychotic agents can cause sedation, respiratory depression, and prolonged QT intervals and may lead to rare but life-threatening neuroleptic malignant syndrome. One of the most common clinical concerns with dexmedetomidine is bradycardia. While bradycardia was commonly seen in several trials, there were no significant differences between the dexmedetomidine and the comparator groups (benzodiazepines, propofol, placebo, and haloperidol) with regards to bradycardia necessitating treatment (*e.g.*, atropine, glycopyrrolate, or pacing).[19,20,64,96,97] Current evidence supports the use of dexmedetomidine for prevention of delirium and for treatment of refractory delirium across a wide variety of ICU patients, including those not on mechanical ventilation, but further studies are needed on dexmedetomidine as the first-line therapy for the treatment of delirium once it develops. Additionally, studies examining the effectiveness of α2-agonists administered orally or by intermittent intravenous bolus (*e.g.*, guanfacine and clonidine) are needed with regard to delirium, as one of the limitations of dexmedetomidine therapy is its administration by continuous infusion. In general, pharmacologic measures should only be considered once nonpharmacologic prevention strategies have failed and the patient is a risk to self or others. Synthesizing the evidence, we recommend

the algorithm in figure 2, built upon the Society of Critical Care Medicine's ABCDEF bundle, for delirium prevention and treatment in the ICU.

Conclusions

Delirium is now recognized to be a common and serious clinical manifestation of acute brain organ dysfunction with long-term consequences. This recognition has led to routine screening and increased attention to prevention. Intensivists now routinely assess for it, and many ICUs around the country are implementing preventative strategies, such as the ABCDEF bundle. While this is a large problem in the ICU, it is increasingly recognized throughout the hospital as patients age and polypharmacy worsens. Preventing delirium will become the responsibility of many clinicians who will have the ability to avoid precipitating factors. Further studies are needed on effective treatments, differences between the motor subtypes, and long-term consequences of ICU delirium.

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Competing Interests

The authors declare no competing interests.

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