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ICU Delirium and ICU-related PTSD

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SYNOPSIS

Delirium is one of the most common behavioral manifestations of acute brain dysfunction in Intensive Care Unit (ICU) and is a strong predictor of worse outcome. Routine monitoring for delirium is recommended for all ICU patients using validated tools (e.g., CAM-ICU, ICDSC). In delirious patients, a search for all reversible precipitants is the first line of action and pharmacological treatment should be considered when all causes have been ruled out, and not contraindicated.

Long-term morbidity, in the forms of cognitive, physical and psychological impairments, has significant consequences for survivors of critical illness and for their caregivers. ICU patients may develop PTSD anchored to their critical illness experience, with ICU-related PTSD incidence rates of 10%. Using ICU diaries during a critical illness may minimize the occurrence of future ICU-related PTSD.

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Keywords

Intensive Care Unit; Delirium; Post-Traumatic Stress Disorder; ICU-related PTSD; Long-term Cognitive Impairment; Brain Dysfunction; Critical Illness

DELIRIUM

One of the most common behavioral manifestations of acute brain dysfunction in Intensive Care Unit (ICU) is delirium. According to the fifth edition of the Diagnostic and Statistical Manual of the American Psychiatric Association (DSM-5), delirium is defined as 1) a disturbance of consciousness (i.e., reduced clarity of awareness of the environment) with reduced ability to focus, sustain, or shift attention, 2) a change in cognition (e.g., memory deficit, disorientation, language disturbance) or development of a perceptual disturbance that is not better accounted for by a preexisting, established, or evolving dementia, 3) that develops over a short period of time, hours to days, and fluctuates over time 4) with evidence from the history, physical examination, or laboratory findings that the disturbance is caused by a direct physiologic consequence of a general medical condition, an intoxicating substance, medication use, or more than one cause (1) (Figure 1).

The true prevalence and magnitude of delirium has been poorly documented because a myriad of terms, such as acute confusional state, ICU psychosis, acute brain dysfunction, and encephalopathy, have been used historically to describe this condition (2). Delirium occurs in up to 60% to 80% of mechanically ventilated medical and surgical ICU patients and 50% to 70% of non-ventilated medical ICU patients (3–7) and should be considered as a significant, serious problem and treated as a possible contributor to mortality risk increased length of mechanical ventilation, longer ICU stays, increased cost, prolonged neuropsychological dysfunction, and mortality (8–12).

Numerous risk factors for delirium have been identified, including pre-existing cognitive impairment, advanced age, use of psychoactive drugs, mechanical ventilation, untreated pain, heart failure, prolonged immobilization, abnormal blood pressure, anemia, sleep deprivation, and sepsis (8, 13–16). The average medical ICU patient has 11 or more risk factors for developing delirium. These risk factors can be divided into predisposing baseline (e.g., demographics, comorbidities) and hospital-related factors (e.g., acute illness severity, medications, ICU events) (Table 1) (17). Delirium prevention in the ICU should focus on reducing the number and duration of potentially modifiable or preventable risk factors. Several mnemonics can aid clinicians in recalling the list of delirium risk factors (Table 2).

Many drugs are considered to be risk factors for the development of delirium. Benzodiazepines have shown a strong association with delirium. The class of benzodiazepines does not seem to change the risk profile, with both lorazepam and midazolam being significant risk factors for delirium. The Society of Critical Care Medicine's (SCCM) ICU Pain Agitation Delirium (PAD) guidelines recommend that non-benzodiazepine sedative options may be preferred over benzodiazepine-based sedative regimens (18). Pandharipande et al. found that every unit dose of lorazepam was associated with a higher risk for daily transition to delirium (19). Similarly, Seymour et al. confirmed

that benzodiazepines are an independent risk factor for development of delirium during critical illness even when given more than 8 hours before a delirium assessment (20). Although targeted pain control has been shown to be associated with improved rates of delirium, Marcantonio found that delirium was significantly associated with postoperative exposure to meperidine, although not to other commonly prescribed opiates (21). Modification of risk factors in the ICU, such as the use of psychoactive drugs, maintenance of sleep/awake cycles, attempts to minimize malnutrition, optimizations of use of restraints, and provision of visual or hearing aids, may decrease the incidence and/or duration of delirium (22).

The consequences of this brain dysfunction are important. Delirium itself is a strong predictor of increased length of mechanical ventilation, longer ICU stays, increased cost, long-term cognitive impairment, and mortality (7, 8, 22–24). Ely et al. showed that over 80% of mechanically ventilated patients developed delirium during their hospital stay. The majority of delirium cases occurred initially in the ICU with an average time of onset between the second and the third day with a mean duration of 3.4 ± 1.9 days. In this study, delirium was the strongest predictor of hospital length of stay, even after adjusting for severity of illness, age, gender, race, and days of psychoactive drug utilization (22).

Delirium has been a strong risk factor for mortality (8, 25). Pisani et al. pointed out that the number of days of ICU delirium was significantly associated with time to death within 1-year post-ICU admission (hazard ratio 1.10, 95% CI: 1.02–1.18) and that the cumulative effect of multiple days is multiplicative rather than additive (25). The relationship between the duration of delirium and mortality was nonlinear, with a greater effect observed earlier in the course of delirium. These data suggest that the harm of delirium may occur early in the period of brain dysfunction for ICU patients (24). Conversely Klein Klouwenberg et al. speculated that the increased mortality could be mediated through a prolonged ICU length of stay, rather than a direct effect on the daily risk of death, though longer duration of delirium (>2 days) still had some attributable mortality risk (26). Nonetheless, a meta-analysis of 28 studies with ICU patients consistently demonstrated a higher risk of in-hospital death associated with delirium (risk ratio 2.19, 95% CI: 1.78–2.70, $P < 0.001$) (27).

In one of the largest multicenter prospective ICU cohorts to date, a longer duration of ICU delirium has been found to be the major independent risk factor for long-term cognitive impairment up to 12 months after surviving a critical illness. This association was found to be independent of severity of illness, sedative or analgesic medication use, age, preexisting cognitive impairment, and co-morbid conditions (28). In this landmark study, the impairment was persistent and no different among medical or surgical ICU populations (29). This work involved ICU patients without acute structural intracranial injury (e.g., no intracranial hemorrhage, no stroke), yet they developed long-term cognitive impairment similar to those with Alzheimer's disease and moderate traumatic brain injury (29). Given delirium is assessable in those with acute structural brain injury (e.g., stroke, trauma), further work is being undertaken (ClinicalTrials.gov Identifier NCT03098459) to understand the interaction between delirium and traumatic brain injury, and their association with long-term cognitive impairment in critically ill trauma survivors (30–32).

Although the mechanisms by which delirium may predispose patients to long-term cognitive impairment after critical illness have not yet been elucidated, delirium appears associated with inflammation and neuronal apoptosis, which may lead to brain atrophy particularly in the frontal lobes and hippocampus (33, 34). White-matter disruption has also been found to be associated with cognitive impairment (35, 36). The pathophysiology of delirium is poorly understood, although a number of different hypotheses exist (37), involving imbalances in neurotransmitters, neuroinflammation, oxidative stress, neuroendocrine, diurnal variation, network connectivity, and large amino acids. None of these theories by themselves probably explains the full phenomenon of delirium but rather two or more of these hypotheses, if not all, act together to lead to the biochemical derangement we know as delirium (38).

Delirium assessment is generally considered a two-step process. The level of arousal to voice is first assessed using a sedation scale, with the particular goal of distinguishing those who are non-comatose and can then be assessed for delirium (i.e., comatose patients are considered unassessable for delirium). The SCCM PAD guidelines recommend the use of the Riker Sedation-Agitation Scale (SAS) or the Richmond Agitation-Sedation Scale (RASS) (18) (Figure 2). The SAS has 7 individual tiers ranging from “1” (unarousable) to “7” (dangerous agitation) (39) while the RASS is a 10-point scale, with four levels of escalating agitation (RASS +1 to +4), one level denoting a calm and alert state (RASS 0), three levels of sedation (RASS -1 to -3), and two levels of coma (RASS -4 to -5). A unique feature of RASS is that it relies on the duration of eye contact following verbal stimulation. The RASS takes less than 20 seconds to perform with minimal training, and has been shown highly reliability among multiple types of healthcare providers with excellent interrater reliability in a broad range of adult medical and surgical ICU patients (40).

Then among non-comatose patients (i.e., equal to or above RASS -3), the next step is to assess for delirium. Several scales have been developed and validated to diagnose delirium in ICU patients (41) [Confusion Assessment Method ICU (CAM-ICU), Delirium Detection Score (DDS), Intensive Care Delirium Screening Checklist (ICDSC), Cognitive Test for Delirium (CTD), Abbreviated Cognitive Test for Delirium, Neelson and Champagne Confusion Scale (NEECHAM), Nursing Delirium Screening Scale (NuDESC)], but the ICDSC and the CAM-ICU are the tools recommended by the SCCM PAD guidelines for this purpose (Figure 3, Table 3). The ICDSC checklist is an eight-item screening tool (one point for each item) that is based on DSM criteria and applied to data that can be collected through medical records or to information obtained from the multidisciplinary team (41). The pooled values for the sensitivity and specificity of the ICDSC are 74% and 81.9%, respectively (41). The CAM-ICU is composed by four features 1) acute onset of mental status changes or fluctuating course; 2) inattention; 3) disorganized thinking; and 4) altered level of consciousness. If the patient manifests both features 1 and 2, plus either feature 3 or 4, the patient is considered CAM positive, and hence positive for delirium. (42). The overall accuracy of the CAM-ICU is excellent, with pooled values for sensitivity and specificity of 80% and 95.9%, respectively (41). The CAM-ICU has been modified and validated in pediatric, emergency department, and neurocritical care populations, as well as translated in over 25 languages (30–32, 43, 44).

Delirium can be categorized into subtypes according to psychomotor behavior. Hyperactive delirium is rare in the pure form and is associated with a better overall prognosis and it is characterized by agitation (i.e. RASS >0), restlessness, and emotional lability (45, 46). Hypoactive delirium, which is very common and often more deleterious for the patient in the long term, is characterized by decreased responsiveness, sedation (i.e., RASS <0), withdrawal, and apathy and remains unrecognized in 66 to 84% of hospitalized patients (14, 45). Another categorization scheme was proposed by Ouimet and colleagues (47), who evaluated 600 ICU patients for symptoms of delirium and categorized them according to the number of symptoms present. Patients with no symptoms were considered to have 'no delirium', those with four or more symptoms to have 'clinical delirium', and those with one to three symptoms to have 'subsyndromal delirium' (48). Subsyndromal delirium has also been associated with post-ICU outcomes (49).

The 2013 PAD guidelines provided an evidence-based road map for clinicians to better manage the intertwined issues of pain, agitation and delirium in critically ill patients (18). The treatment of underlying medical conditions and non-pharmacological issues, like noise, light, sleep and mobility, are cardinal aspects of delirium management. To improve ICU patient outcomes, including with respect to delirium, an evidence-based organizational approach referred to as the ABCDEF bundle (**A**ssess for and manage pain, **B**oth Spontaneous Awakening Trials (SAT) & Spontaneous Breathing Trials (SBT), **C**hoice of appropriate sedation, **D**elirium monitoring, and **E**arly mobility and exercise, **F**amily engagement) has been proposed (50).

Assess for and manage pain

Pain assessment is the first step in proper pain relief and could be very important in patients with delirium. ICUs commonly use patient self-report of pain, like the 1–10 numerical rating scale (NRS) (18). If the patient is unable to self-report, observable behavioral and physiological indicators become important indices for the assessment of pain (51). The Behavioral Pain Scale (BPS) and the Critical-Care Pain Observation Tool (CPOT) are the most valid and reliable behavioral pain scales for ICU patients unable to communicate. According to ICU PAD Guidelines pain medications should be routinely administered in the presence of significant pain (i.e., NRS >4, BPS >5, or CPOT >3) and prior to performing painful invasive procedures (18).

Both SAT & SBT

Protocolized target-based sedation and daily spontaneous awakening trials reduce the number of days of mechanical ventilation (52–54). This strategy also exposes the patient to smaller cumulative doses of sedatives. Spontaneous breathing trials were shown to be superior to other varied approaches to ventilator weaning (12). Thus, incorporation of spontaneous breathing trials into practice has reduced the total time of mechanical ventilation. The awakening and breathing controlled trial combined spontaneous awakening trials with spontaneous breathing trials, and showed shorter duration of mechanical ventilation, a four-day reduction in hospital length of stay, a remarkable 15% decrease in 1-year mortality, and no long-term neuropsychological consequences of waking patients during critical illness (55).

Choice of appropriate sedation

The SCCM PAD guidelines emphasize the need for goal-directed delivery of psychoactive medications to avoid over-sedation, to promote earlier extubation, and the use of sedation scales (SAS, RASS) to help the medical team agree on a target sedation level for each individual patient (18). Numerous studies have identified that benzodiazepines are associated with worse clinical outcomes. The Maximizing Efficacy of Targeted Sedation and Reducing Neurological Dysfunction (MENDS) study showed that patients treated with dexmedetomidine had more days alive without delirium or coma (7.0 vs. 3.0 days; $P = 0.01$), with a lower risk for delirium developing on subsequent days (56). In patients sedated with dexmedetomidine compared with midazolam, the SEDCOM trial (Safety and Efficacy of Dexmedetomidine Compared with Midazolam) showed a reduction in the prevalence of delirium (76.6% vs. 54% with risk of difference 22.6%, 95% CI: 14–33%, $p < 0.001$) and a reduction in the duration of mechanical ventilation (57). However, few studies have directly compared dexmedetomidine to propofol. The PRODEX study showed no difference in delirium outcomes, though delirium was measured only at a single time point after discontinuation of sedation (58). On the other hand, Djaiani et al. recently showed that dexmedetomidine reduced delirium incidence in cardiac surgical patients in the ICU as compared to propofol (59), while Su et al. showed a reduction in patients treated with dexmedetomidine in non-cardiac surgical patients admitted to the ICU (60). There is an ongoing trial (MENDS II study) to determine the best sedative medication to reduce delirium and improve survival and long-term brain function in the ventilated septic patient (ClinicalTrials.gov Identifier: NCT01739933).

Delirium management

An important third element in the PAD guidelines is monitoring and management of delirium by using validated tools (CAM-ICU, ICDSC), as described in detail previously (18). A mnemonic can aid clinicians recalling strategies to consider when delirium is present **DR DRE** (**D**isease **R**emediation, **D**rug **R**emoval, **E**nvironmental modifications). In delirious patients, a search for all reversible precipitants is the first line of action and pharmacological treatment should be considered when all other causes are ruled out and not contraindicated (22) (Figure 4). The 2013 SCCM PAD Guidelines recommend non-pharmacologic approaches to reduce the incidence and duration of ICU delirium, and to improve functional outcomes, such as using early and progressive mobilization, promoting sleep hygiene with control of light, noise, and physical stimuli, and clustering patient care activities.

Antipsychotics, especially haloperidol, are commonly administered for the treatment of delirium in critically ill patients. However, evidence for the safety and efficacy of antipsychotics in this patient population is lacking; hence, the 2013 PAD guidelines did not include specific recommendations for using any particular medication (18). Since the lack of evidence about the efficacy of typical versus atypical antipsychotics, Ely et al. are conducting the MIND-USA (Modifying the Impact of ICU-Induced Neurological Dysfunction-USA) Study (ClinicalTrials.gov Identifier NCT01211522) to define the role of this drugs in the management of delirium and on short- and long-term clinical outcomes in vulnerable critically ill patients (61). Delirium prophylaxis with medications is discouraged in the PAD guidelines, but recent small studies on delirium prophylaxis with antipsychotics

showed that a low-dose of haloperidol may reduce the incidence of delirium in ICU patients (62, 63). By contrast, the HOPE-ICU randomized controlled trial showed no benefit of haloperidol administration for delirium prophylaxis in a mixed population of medical and surgical adult ICU patients (64).

Exercise and early mobility

Early mobility is an integral part of the ABCDEF bundle. During ICU stay critically ill patients can lose up to 25% peripheral muscle weakness within 4 days when mechanically ventilated and 18% in body weight by the time of discharge and this process is higher in the first 2–3 weeks of immobilization.(65) The consequence of physical dysfunction in critically ill patients can be profound and long-term with significant reduction in functional status being observed even 1 year and 5 years after ICU discharge (66–68). Morris et al. showed that initiating physical therapy early during the patient's ICU stay was associated with decreased length of stay both in the ICU and in the hospital (65). Schweickert et al. showed in mechanically ventilated patients that a daily SAT, plus physical and occupational therapy, resulted in an improved return to independent functional status at hospital discharge, shorter duration of ICU-associated delirium, and more days alive and breathing without assistance(69). Although all these studies demonstrated feasibility of physical therapy, it may more effective to start physical therapy early in the ICU course.

A better understanding of the underlying risk factors for disability following critical illness and of the effect that activity, during hospitalization, may have on outcomes is needed. Brummel et al. designed the Masuring OutcomeS of Activity in Intensive Care (MOSAIC) observational study to evaluate the relationship between activity in the hospital, measured by using a clinical mobility scale and accelerometry, and disability, physical function, and cognitive function in survivors of critical illness 3 and 12 months after ICU discharge (ClinicalTrials.gov Identifier NCT).

Family engagement

Critical illness usually impacts not only an individual, but their entire support system, which may or may not be their nuclear family, or some combination of family and friends or other caregivers who are actively engaged in supportive roles. In light of this, it is crucial not only to recognize the needs of the patient, but to identify and address the needs of their family as well. Family members and surrogate decision makers must become active partners in multi-professional decision-making and care (70).

POST-TRAUMATIC STRESS DISORDER (PTSD)

Post-traumatic stress disorder (PTSD), depression, and anxiety are important mental health problems after critical illness (71–73). PTSD is a serious psychiatric disorder that can occur in people who have experienced or witnessed a traumatic event (e.g., natural disaster, a serious accident, a terrorist act, war/combat, rape or other violent personal assault) (1), like surviving a critical illness. Common screening tools include PCL-5 (PTSD Checklist for DSM-5), and IES (Impact of Events Scale), but often require extensive confirmation using

diagnostic tools like DSM-5 and CAPS (Clinician Administered PTSD Scale) (74–76). These complexities probably relate to the inconsistent epidemiology of ICU-related PTSD.

The incidence of PTSD, anchored to the ICU experience and not related to past stressful experiences, has been consistently around 10% in the first year after hospital discharge (73, 74, 77, 78) in the most rigorous studies, despite historically reported higher rates in many other studies (75, 76). It is critically important to recognize despite these reports of higher epidemiologic occurrences of PTSD after critical illness(76), many studies have not distinguished pre-existing PTSD from ICU-related PTSD, nor used DSM criteria, or accounted for the ICU course. Using a multicenter ICU population of US civilians and veterans, the most recent study to clearly identify ICU-related PTSD demonstrated an occurrence of 1 in 10 ICU survivors (74).

It has been suggested that the quality of cognitive processing at the time of the traumatic event is important in the development of PTSD. Those individuals who report feeling confusion and feeling overwhelmed as they experienced the traumatic situation are more likely to suffer from PTSD (79). ICU patients may be predisposed to PTSD because during the traumatic event, either due to the treatment(s) instituted during the ICU stay or due to the critical illness. Ultimately, their ability to process information is likely to be compromised (80).

One risk factor for the development of PTSD/PTSD-related symptoms may include early recall of delusional memories. The number of early recall of delusional memories, without any factual memories, has been related with increased the risk of developing PTSD and high severity of PTSD-related symptoms (81, 82). Granja et al. found that amnesia, for the early period of critical illness, was positively associated with the level of PTSD-related symptoms (80). However, given that in-ICU amnesia was also associated with longer ICU length of stay, greater illness severity, and greater previous hospital admissions, the authors suggested that ICU-amnesia might be rather a proxy for trauma severity of disease and that adverse experiences during ICU stay may lead to higher levels of PTSD-related symptoms (80). Weinert and Sprenkle found that delirious memories were associated with more PTSD-like symptoms, but patients who were the most awake during mechanical ventilation also had the lowest levels of PTSD-like symptoms (83).

Patients with a history of depression and related disorders may also be at risk of developing PTSD (74, 84). Depression can have emotional, psychological, psychosocial, and physical effects that diminish coping mechanisms. Bienvenu and Patel et al. both independently found that previous history of depressive illness was a significant predictor of risk for post-ICU PTSD (74, 85). Similarly, Cuthbertson et al. found that treatment-seeking behaviors for psychological distress prior to ICU predicted eventual development of PTSD (86). However these studies assessed previous psychiatric history using retrospective accounts, and it could be questioned if the self-reports of previous psychopathology may have been increased by current psychological distress (87).

Attention has been focused on the type and duration of ICU sedation, as it relates to risk of post-ICU PTSD, but the data has been conflicting and non-confirmatory. Particular interest

has been placed on the role of benzodiazepines (19, 88). Both midazolam (89), lorazepam (88), and opiates administered in the ICU have been found to have links to post-ICU PTSD (85). Conversely from one of the largest, comprehensive, and current ICU-related PTSD studies, no association was found between PTSD and duration of delirium, benzodiazepine dose, or opiate dose (74). Despite these being modifiable risk factors, especially for ICU providers to consider, the analgo-sedative classes have no clear relationship with ICU-related PTSD.

The impact of sedation interruption or minimizing sedation on post-ICU PTSD risk remains unclear, but potential benefits of minimizing sedation seem to outweigh the potential harm. Protocol-driven sedation interruptions may actually reduce PTSD symptoms after ICU care, despite old-standing beliefs stating otherwise. The possibility of post-ICU PTSD symptom reduction is promising and provides yet another reason for physicians to employ a goal-directed approach to sedation (52, 55, 90).

Exploration of the role of genetics in post-ICU PTSD has provided interesting insights into non-modifiable factors that potentially influence the occurrence of symptoms among survivors of critical illness. An investigation in cardiac surgery patients requiring ICU care demonstrated increased symptoms of PTSD among individuals homozygous for a single-nucleotide polymorphism of the glucocorticoid receptor gene (91). Another study of mixed ICU patients revealed an association between homozygosity for a single nucleotide polymorphism of the corticotrophin-releasing hormone binding protein and decreased post-ICU PTSD symptoms (92). Although genetic polymorphisms are not modifiable, they may offer future targets to assist in identification of patients at higher risk (93).

Several medications have been studied to potentially prevent PTSD. The protective effects of hydrocortisone (94, 95) on PTSD development were observed in acutely trauma-exposed patients in the emergency department (ED), in which treatment was initiated within 6 to 12 hours post trauma. Some evidences showed that low serum cortisol is predictive of the development of post-ICU PTSD (96), therefore, stress dose hydrocortisone may offer protective effects. Kok et al. conversely showed that exogenous administration of the glucocorticoid receptor agonist dexamethasone, compared with placebo, during cardiac surgery does not influence the prevalence of posttraumatic stress disorder and depression (97). Currently, pharmacologic interventions, like glucocorticoids, are not a mainstay prophylactic or intervention therapy against ICU-related PTSD.

Intranasal administration of the neuropeptide oxytocin may be a promising pharmacological agent to prevent PTSD (98, 99). Evidence from studies in animals and in healthy and psychiatric human populations have shown that oxytocin administration may modulate glucocorticoid and autonomic stress reactivity (100, 101), dampen anxiety, and alter neural threat processing (102, 103). However after exposure to trauma, oxytocin administration showed detrimental effects increasing amygdala reactivity to fearful faces and decreasing amygdala-ventrolateral prefrontal functional connectivity (104). Moreover other studies indicate that the effects of a single oxytocin administration may differ from the effects of repeated administration; the latter may be required to achieve clinically relevant effects

regarding the prevention of PTSD (104). Therefore, oxytocin remains investigational with respect to ICU-related PTSD.

The fragmentary nature of memories of the ICU experience and the high proportion of delusional memories that are recalled afterwards make it difficult for patients to make sense of what has happened to them (105). These altered memories may be a major precipitant of PTSD in this population (77, 82). Minimizing the occurrence of delusional memories in the ICU poses a significant clinical challenge. However, interventions focused on improving patient understanding of events occurring during critical illness have provided promising results (93). For example, all procedures should be explained to patients and their families, and the patient should be reoriented with each physical intervention, even if the patient appears to be heavily sedated. Another possible adjunct to decrease post-ICU complications entails family integration into ICU care, as much as possible (106).

Jones et al. evaluated the influence of ICU diaries on symptoms of post-ICU posttraumatic stress, among both patients and their family members, after 3 months from ICU discharge. Patients in intervention arm received their ICU diary at 1 month following critical care discharge and the final assessment of the development of acute PTSD was made at 3 months. The incidence of new cases of PTSD was reduced in the intervention group compared to the control patients (5% versus 13%, $P = 0.02$) (78). Diaries are a low-risk intervention that can probably help ICU patients to change how they think about their illness as they reread the story and build an autobiographical memory.

Families may also be helped because the diaries help to facilitate communication with the ICU patient about their treatment and writing in the diary may allow them to express some their feelings. A strong relation has been found between high levels of PTSD-related symptoms in family members and those in ICU survivors. So, an ICU diary that is shared between the patient and their family, may be better than one that just concentrates on the patient (78). Similarly Garrouste-Orgeas et al. assessed the influence of ICU diaries, written by family members, nurses, and physicians on ICU survivors (107). At the time of ICU discharge diaries were provided to survivors and to relatives. For both patients and relatives, levels of posttraumatic symptoms measured by the IES-R were lower at 12-month follow-up, when compared to pre- and post-diary controls (107). ICU diaries have also been associated with reductions in related post-ICU psychiatric morbidities, including depressive and anxiety symptoms (108).

Similar to diaries/journals, a single counseling session has been shown to increase both patient and family coping ability after an ICU stay (82). Both may also prevent, reduce, or help treat PTSD (106). Other studies suggest that music, nature sounds, various forms of massage and reflexology could all be employed to reduce acute stress among ICU patients, including mechanically ventilated patients (109). As acute stress is an important precursor of long-term psychological morbidity such as PTSD, these short-term practices could also have an impact on long-term outcome. The risk of harm from such therapies is not generally high, but protocols and training for staff are needed (109). Although several of these alternative risk factors have been identified, more work need to be done to identify whether individual

difference variables may play a role in how people cope with the stress of the ICU (Figure 5).

In general, broader personality traits have been associated with greater resilience to PTSD, including extraversion and conscientiousness, whereas neuroticism and negative emotionality have been positively associated with PTSD development (87). Social support may play an important protective role against the development of PTSD (110). One study found that social support was significantly negatively associated with PTSD symptoms in a sample of ICU patients admitted for ARDS. This association in ICU-treated individuals between social support and decreased psychological distress could represent an important topic for future research (87, 93).

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KEY POINTS

- Delirium is a strong predictor of increased length of mechanical ventilation, longer ICU stays, increased cost, long-term cognitive impairment, and mortality.
- Routine monitoring for delirium is recommended for all ICU patients.
- In delirious patients, pharmacologic treatment should be used only after giving adequate attention to correction of modifiable contributing factors. The ABCDEF bundle (Attention to analgesia, Both awakening and breathing trials, Choosing right sedative, Delirium monitoring and management, Early exercise and Family involvement) is recommended and associated with improved outcomes including reduction in delirium.
- PTSD is one of many important mental health problems after significant critical illness.
- The incidence of ICU-related PTSD is around 10% and using ICU diaries into routine clinical care may alter PTSD outcomes among both patients and families.

Figure 1.

Cardinal symptoms of delirium. From Morandi et al. Understanding international differences in terminology for delirium and other types of acute brain dysfunction in critically ill patients. *Intensive Care Med.* 2008 Oct;34(10):1907–15, with permission.

Morandi et al. Understanding international differences in terminology for delirium and other types of acute brain dysfunction in critically ill patients. *Intensive Care Med.* 2008 Oct; 34(10):1907–15. doi: 10.1007/s00134-008-1177-6. Epub 2008 Jun 18. (2)

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RASS	SAS
+4 Combative Combative, violent, immediate danger to staff	7 Dangerous Agitation Pulling at ET tube, trying to remove catheters, climbing over bedrail, striking at staff, trashing side-to-side
+3 Very Agitated Pulls to remove tubes or catheters; aggressive	6 Very Agitated Requiring restraint and frequent verbal reminding of limits, biting ETT
+2 Agitated Frequent non-purposeful movement, fights ventilator	6 Very Agitated Requiring restraint and frequent verbal reminding of limits, biting ETT
+1 Restless Anxious, apprehensive, movements not aggressive	5 Agitated Anxious or physically agitated, calms to verbal instructions
0 Alert and Calm Spontaneously pays attention to caregiver	4 Calm and Cooperative Calm, easily arousable, follows commands
-1 Drowsy Not fully alert, but has sustained awakening to voice - eye opening and contact >10 seconds	3 Sedated Difficult to arouse but awakens to verbal stimuli or gentle shaking, follows simple commands but drifts off again
-2 Light Sedation Briefly awakens to voice - eyes open and contact <10 seconds	3 Sedated Difficult to arouse but awakens to verbal stimuli or gentle shaking, follows simple commands but drifts off again
-3 Moderate Sedation Movement or eye opening to voice - no eye contact	3 Sedated Difficult to arouse but awakens to verbal stimuli or gentle shaking, follows simple commands but drifts off again
-4 Deep Sedation No response to voice, but movement or eye opening to physical stimulation	3 Sedated Difficult to arouse but awakens to verbal stimuli or gentle shaking, follows simple commands but drifts off again 2 Very Sedated Arouses to physical stimuli but does not communicate or follow commands, may move spontaneously
-5 Unarousable No response to voice or physical stimulation	1 Unarousable Minimal or no response to noxious stimuli, does not communicate or follow commands

<http://www.icudelirium.org>

Figure 2.
Richmond Agitation-Sedation Scale (RASS) and Riker Sedation-Agitation Scale (SAS).
Data from Babar A. Khan, Oscar Guzman, Noll L. Campbell, et al. Comparison and Agreement Between the Richmond Agitation-Sedation Scale and the Riker Sedation-Agitation Scale in Evaluating Patients' Eligibility for Delirium Assessment in the ICU. Chest. Volume 142, Issue 1, July 2012, Pages 48–54.

Figure 3.
Confusion Assessment Method for the ICU (CAM-ICU). From http://www.icudelirium.org/docs/CAM_ICU_training.pdf, page 8.

Figure 4.
Sample Delirium Protocol. From <http://www.icudelirium.org/delirium/management.html>.

Figure 5.

Risk factors for post-ICU psychological outcome. From McGiffin JN et al., Is the intensive care unit traumatic? What we know and don't know about the intensive care unit and posttraumatic stress responses. *Rehabilitation Psychology*, Vol 61(2), May 2016, 120–131, with permission.

ICU Intensive Care Unit, PTSD Posttraumatic stress disorder.

McGiffin JN et al., Is the intensive care unit traumatic? What we know and don't know about the intensive care unit and posttraumatic stress responses. *Rehabilitation Psychology*, Vol 61(2), May 2016, 120–131. <http://dx.doi.org/10.1037/rep0000073>, American Psychological Association, (87).

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Table 1

Risk Factors for Delirium

	Unmodifiable/Unpreventable Risk Factors	Potentially Modifiable/Preventable Risk Factors
Baseline Risk Factors	Age APOE-4 genotype History of Hypertension Pre-existing cognitive impairment History of Alcohol Use History of Tobacco Use History of Depression	Sensory deprivation (e.g., Hearing or Vision Impairment)
Hospital-Related Risk Factors	High Severity of Illness Respiratory Disease Need for mechanical ventilation Number of infusing medications Elevated inflammatory biomarkers High LNAA metabolite levels	Anemia Acidosis Hypotension Infection/Sepsis Metabolic disturbances Fever Lack of visitors Sedatives/Analgesics Immobility Bladder catheters Vascular catheters Gastric tubes Sleep & Light deprivation

Abbreviations: APOE-4: apolipoprotein-E4 polymorphism; LNAA: Large neutral amino acids

Adapted from Brummel NE, Girard TD. Preventing delirium in the intensive care unit. Crit Care Clin. 2013 Jan;29(1):51–65, with permission.

Table 2**Mnemonics for Risk Factors for Delirium**

I WATCH DEATH		DELIRIUM (S)	
I	Infection: HIV, sepsis, Pneumonia	D	Drugs
W	Withdrawal: Alcohol, barbiturate, sedative-hypnotic	E	Eyes, ears, and other sensory deficits
A	Acute metabolic: Acidosis, alkalosis, electrolyte disturbance, hepatic failure, renal failure	L	Low O2 states (e.g. heart attack, stroke, and pulmonary embolism)
T	Trauma: Closed-head injury, heat stroke, postoperative, severe burns	I	Infection
C	CNS pathology: Abscess, hemorrhage, hydrocephalus, subdural hematoma, Infection, seizures, stroke, tumors, metastases, vasculitis, Encephalitis, meningitis, syphilis	R	Retention (of urine or stool)
H	Hypoxia: Anemia, carbon monoxide poisoning, hypotension, Pulmonary or cardiac failure	I	Ictal state
D	Deficiencies: Vitamin B12, folate, niacin, thiamine	U	'Under'hydration/'under' nutrition
E	Endocrinopathies: Hyper/hypoadrenocorticism, hyper/hypoglycemia, Myxedema, hyperparathyroidism	M	Metabolic causes (DM, Post-operative state, Sodium abnormalities)
A	Acute vascular: Hypertensive encephalopathy, stroke, arrhythmia, shock	(S)	Subdural hematoma
T	Toxins or drugs: Prescription drugs, illicit drugs, pesticides, solvents		
H	Heavy Metals: Lead, manganese, mercury		

Adapted from Saint Louis University Geriatrics Evaluation Mnemonics Screening Tools (SLU GEMS). Developed or compiled by: Faculty from Saint Louis University Geriatrics Division and St. Louis Veterans Affairs GRECC and <http://pda.mao.ca/content/causes-delirium>.

Table 3

Intensive Care Delirium Screening checklist (ICDSC).

Intensive Care Delirium Screening Checklist Worksheet (ICDSC)	No 0	Yes 1
1. Altered Level of Consciousness		
Deep sedation/coma over entire shift [SAS= 1, 2; RASS = -4, -5] = Not assessable Agitation [SAS = 5, 6, or 7; RASS= 1-4] at any point = 1 point Normal wakefulness [SAS = 4; RASS = 0] over the entire shift = 0 points Light sedation [SAS = 3; RASS= -1, -2, -3]: = 1 point (if no recent sedatives) = 0 points (if recent sedatives)		
2. Inattention		
Difficulty following instructions or conversation, patient easily distracted by external stimuli Will not reliably squeeze hands to spoken letter A: SAVEA HAART		
3. Disorientation		
In addition to name, place, and date, does the patient recognize ICU caregivers? Does patient know what kind of place they are in?		
4. Hallucination, delusion, or psychosis		
Ask the patient if they are having hallucinations or delusions. (e.g. trying to catch an object that isn't there). Are they afraid of the people or things around them?		
5. Psychomotor agitation or retardation		
Either: a) Hyperactivity requiring the use of sedative drugs or restraints in order to control potentially dangerous behavior (e.g. pulling IV lines out or hitting staff) OR b) Hypoactive or clinically noticeable psychomotor slowing or retardation		
6. Inappropriate speech or mood		
Patient displays: inappropriate emotion; disorganized or incoherent speech; sexual or inappropriate interactions; is either apathetic or overly demanding		
7. Sleep-wake cycle disturbance		
Either: frequent awakening/< 4 hours sleep at night OR sleeping during much of the day		
8. Symptom Fluctuation		
Fluctuation of any of the above symptoms over a 24 hr period.		
Total shift score (0-8)		

Normal 0; Delirium 4-8; Subsyndromal Delirium 1-3

Score your patient over the entire shift. Components don't all need to be present at the same time. Components 1 through 4 cannot be completed when the patient is deeply sedated or comatose (ie. SAS = 1 or 2; RASS = -4 or -5); Components 5 through 8 are based on observations throughout the entire shift. Information from the prior 24 hrs should be obtained for components 7 and 8.

Adapted from: Bergeron et al. Intens Care Med 2001;27:859-64; Ouimet et al. Intens Care Med 2007;33:1007-13.