Sedation and Delirium

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Case Presentation

A 74-year-old man with a history of coronary artery disease, congestive heart failure, hypertension, and atrial fibrillation presented with 12 h of progressive shortness of breath, chest pressure, and cough. At the time of presentation, he was tachycardic (HR 148), tachyneac (RR 38), hypoxemic (SaO_2 initially 78 % on room air), and struggling to breathe (demonstrated by use of accessory muscles and shallow breaths). Chest x-ray was consistent with bilateral pulmonary edema, B-type natriuretic peptide (BNP) was 8 times the upper limit of normal, and ECG showed rapid atrial fibrillation without ST segment changes. In addition to supplemental oxygen, furosemide, morphine, and aspirin, continuous positive airway pressure (CPAP) was initiated and SaO_2 improved to 89 % on 100 % FiO_2. The patient, however, became confused and agitated, which progressed after receipt of additional doses of morphine. In his confused state, the patient removed the CPAP mask on multiple occasions, with each event causing declines in SaO_2, so the patient was intubated and invasively mechanically ventilated while being sedated with a continuous midazolam infusion. He was transferred from the Emergency Department to the ICU.

Question What is the best approach to managing this patient's sedation and delirium?

Answer Close monitoring, minimizing sedation, and eliminating risk factors for delirium.

Critically ill patients, especially those who are mechanically ventilated, frequently experience pain, anxiety, and/or agitation, prompting treatment with analgesics and sedatives. Care should be taken when administering these medications since oversedation and delirium are common in the ICU, where they are associated with poor outcomes. After transfer to the ICU, midazolam was discontinued, and intermittent fentanyl boluses were used to treat pain in lieu of morphine after labs revealed acute kidney injury. Depth of sedation was monitored every 2 h (and when sedating medications were given) using the Richmond Agitation-Sedation Scale (RASS), and the patient was assessed for delirium every 8 h with the Confusion Assessment Method for the ICU (CAM-ICU). During the first 6 h after transfer to the ICU, the fentanyl dose and frequency were increased due to ongoing pain and agitation, and propofol was started and titrated with a goal of achieving a target RASS of −1 (drowsy) or 0 (alert and calm). By the next morning, RASS was consistently either −2 (light seda-

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R.C. Hyzy (ed.), *Evidence-Based Critical Care*, DOI 10.1007/978-3-319-43341-7_27

tion) or −1 (drowsy), but the patient remained delirious (CAM-ICU positive). Ongoing treatment for acute exacerbation of congestive heart failure included volume control ventilation with low tidal volumes (6 mL/kg ideal body weight) and FiO_2 and PEEP titrated to maintain $SaO_2 > 89\%$. Intermittent furosemide was continued, leading to significant diuresis and improved oxygenation. Daily spontaneous awakening trials (SATs) were paired with spontaneous breathing trials (SBTs) each morning that safety screens were passed, and physical and occupational therapy were initiated early. One hour into an SAT on the first full ICU day, propofol was restarted at 1/2 the previous dose due to recurrence of agitation. Propofol was held again during an SAT on the second ICU day and was not subsequently restarted. Similarly, intermittent fentanyl boluses were held and no longer needed by the second ICU day. The patient remained comfortable without sedation through the third ICU day, when he passed an SBT, was alert, non-delirious (CAM-ICU negative), had a strong cough and minimal secretions, and was successfully extubated. The next day, he was transferred out of the ICU to the general medical ward.

Principles of Management

Monitoring Sedation and Delirium

Two sedation scales—the RASS [1, 2] (Fig. 27.1; used in this case) and the Sedation-Agitation Scale (SAS) [3]—are well-validated for use in the ICU and are therefore recommended in the 2013 Society of Critical Care Medicine (SCCM) guidelines for the management of pain, agitation, and delirium in the ICU [4] (Table 27.1). By giving ICU practitioners a reliable means by which to assess, describe, and document a patient's level of consciousness, these tools can improve patient care. Multiple randomized trials have shown that a protocol guided by a validated sedation scale improves outcomes, including duration of mechanical ventilation [5, 6].

The SCCM guidelines (Table 27.1) also recommend monitoring ICU patients for delirium using one of two validated tools: the CAM-ICU [7] (Fig. 27.2; used in this case) or the Intensive Care Delirium Screening Checklist (ICDSC) [8]. Delirium, which is frequently hypoactive (i.e., characterized by somnolence rather than agitation) in the ICU, is easily overlooked when a validated assessment tool is not used. Use of the CAM-ICU or ICDSC, therefore, can improve detection and management of delirium.

Minimizing Sedation

Oversedation is common and harmful in the ICU, where heavily sedated patients remain on the ventilator longer and have higher mortality rates than their less sedated counterparts [9]. Patients who require sedatives during critical illness should therefore be managed with light rather than heavy sedation (barring a specific, time-limited indication for the latter, e.g., neuromuscular blockade, open abdomen, etc.). Use of a validated sedation scale (see section on "Sedative Choice") is an important part of efforts to maintain light sedation, since frequent, reliable data regarding actual vs. targeted level of sedation can prompt changes in sedative choice, dose, and/or frequency. In addition to use of sedation scales, strategies that can improve outcomes by minimizing sedation include treating pain adequately before using sedatives [10], avoiding benzodiazepines in favor of other sedatives (e.g., propofol, dexmedetomidine, and/or an opioid) [11], using a sedation protocol [5], and interrupting sedatives on a daily basis with SATs [12, 13].

Risk Factors for Delirium

Though questions remain regarding the most effective strategies to prevent and treat delirium (see Prevention of Delirium and Antipsychotics sections), studies have identified a number of modifiable risk factors for delirium that should be addressed whenever possible when managing patients who are high

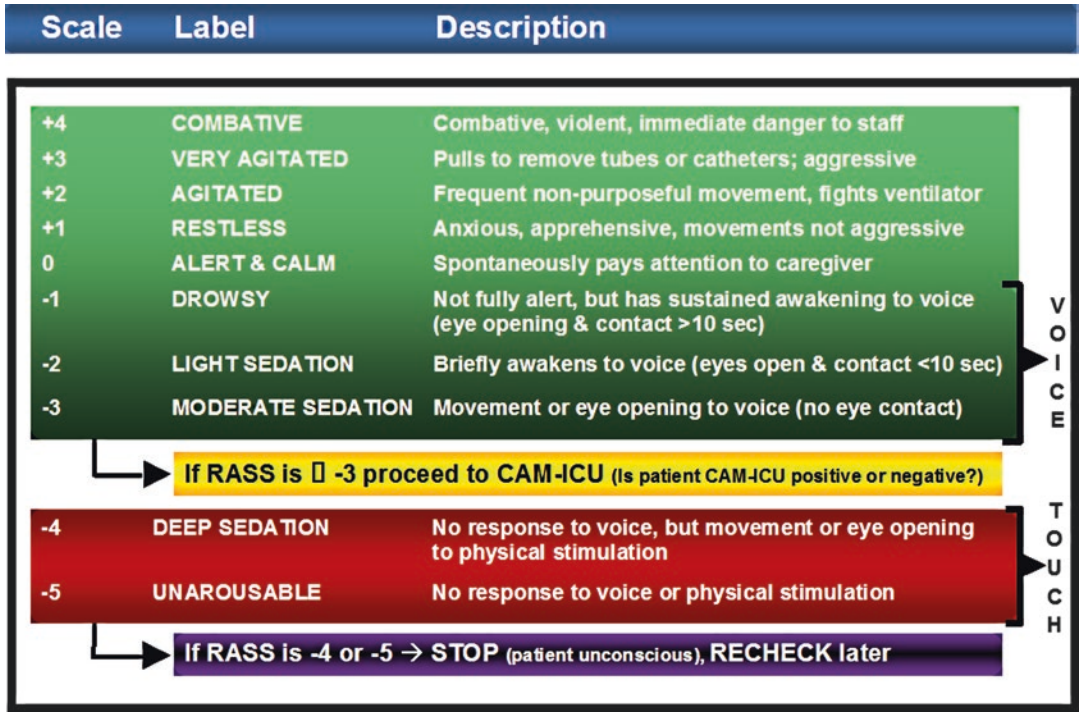

Fig. 27.1 Richmond Agitation-Sedation Scale (© Vanderbilt University)

Table 27.1 The ICU pain, agitation, and delirium care bundle

Component	Pain	Agitation	Delirium
Assess	Assess ≥4×/shift and prn NRS if patient can report pain BPS or CPOT if patient cannot report	Assess ≥4×/shift and prn RASS or SAS if not paralyzed Brain function monitor if paralyzed	Assess delirium each shift and prn CAM-ICU or ICDSC
Treat	Treat pain then reassess Non-pharmacologic (relaxation) IV opioids +/– non-opioids for non-neuropathic pain Gabapentin or carbamazepine for neuropathic pain	Targeted sedation and/or daily SATs to achieve goal of RASS −1 to 0 or SAS 3 to 4 If undersedated, use non-benzodiazepine sedatives as needed If oversedated, hold sedatives	Treat pain as needed Reorient patients; provide eyeglasses, hearing aids as needed Avoid benzodiazepines unless alcohol or benzodiazepine withdrawal Avoid rivastigmine Avoid antipsychotics if QTc is high
Prevent	Preprocedural analgesia Relaxation therapy	Treat pain before using sedation Consider daily SBTs and early mobility unless contraindicated EEG if high ICP warrants burst suppression or high risk for seizures	Identify delirium risk factors Avoid benzodiazepines Early mobility Promote sleep Restart baseline psychiatric medications if indicated

This table modifies and summarizes the full bundle described in Barr et al. [4]
Abbreviations: *BPS* Behavioral Pain Scale, *CAM-ICU* Confusion Assessment Method for the Intensive Care Unit, *CPOT* Critical-Care Pain Observation Tool, *EEG* electroencephalogram, *ICDSC* Intensive Care Delirium Screening Checklist, *ICP* intracranial pressure, *IV* intravenous, *NRS* numeric rating scale, *RASS* Richmond Agitation-Sedation Scale, *SAS* Sedation Agitation Scale, *SATs* spontaneous awakening trials, *SBTs* spontaneous breathing trials

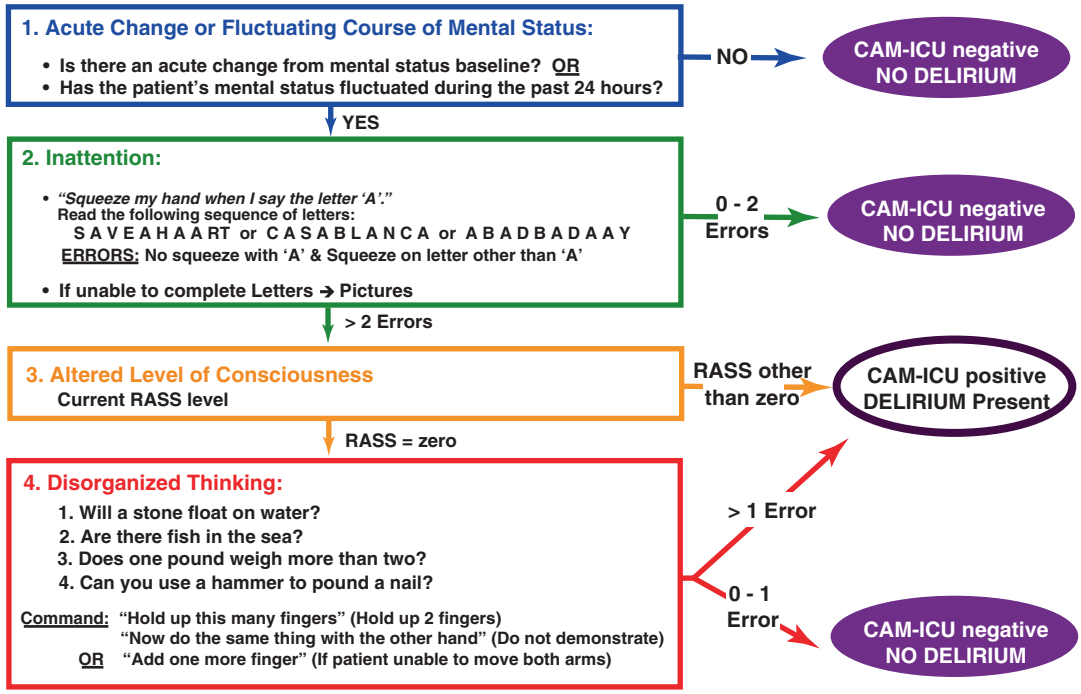

Fig. 27.2 CAM-ICU (© 2002 Vanderbilt University)

risk as well as those already delirious. Numerous observational and interventional studies have found benzodiazepines (used initially in this case) increase delirium risk [14, 15], whereas dexmedetomidine does not [16, 17]. This may be because benzodiazepine pharmacokinetics make them prone to cause oversedation—drug-induced coma, regardless of which medication is the culprit, is a delirium risk factor—or because of their mechanism of action in the brain (GABA agonism). Infection, acute kidney injury, metabolic acidosis, mechanical ventilation, and high severity of illness are also risk factors for delirium that, in many cases, can be addressed [18].

In addition to the modifiable risk factors listed herein, many risk factors for delirium are not modifiable but an awareness of these factors may prompt clinicians to monitor high-risk patients more closely for delirium. These include advanced age and hypertension (both present in this case) as well as preexisting cognitive impairment, emergency surgery, and trauma.

Evidence Contour

This case highlights a number of evidence gaps and areas of controversy that remain despite the growing body of evidence regarding sedation and delirium in the ICU.

Sedative Choice

Dozens of randomized controlled trials have examined whether sedative choice affects outcomes in the ICU. Most compared a benzodiazepine (typically midazolam), the class of sedatives used most frequently in the ICU for several decades, with a non-benzodiazepine sedative, and the large majority of these trials found non-benzodiazepine sedation resulted in better outcomes (Table 27.2). A recent meta-analysis, in fact, found that benzodiazepine sedation (compared with sedation using propofol or dexmedetomidine) delays extubation and discharge from the ICU [11]. These data led the SCCM guidelines [4]

Table 27.2 Randomized trials comparing benzodiazepines with alternative sedatives in the ICU

First author	Year	Population	Outcome(s) improved
Benzodiazepines vs. propofol			
Trials finding better outcomes with propofol			
Grounds RM	1987	Cardiac surgery	Faster awakening
Aitkenhead AR	1989	General ICU	More consistent awakening, faster weaning
McMurray TJ	1990	Cardiac surgery	Faster awakening
Carrasco G	1993	General ICU	More accurate sedation, faster awakening, lower costs
Roekaerts PM	1993	Cardiac surgery	Faster awakening, earlier extubation
Ronan KP	1995	Surgical ICU	Faster awakening
Sherry KM	1996	Cardiac surgery	Lower costs
Chamorro C	1996	General ICU	Better ventilator synchrony, faster awakening
Barrientos-Vega R	1997	General ICU	Earlier extubation
Weinbroum AA	1997	General ICU	Faster awakening
Sanchez-Izquierdo-Riera JA	1998	Trauma ICU	Faster awakening
McCollam JS	1999	Trauma ICU	Less oversedation
Hall RI	2001	Mixed ICU	More accurate sedation, earlier extubation
Carson SS	2006	Medical ICU	Fewer ventilator days
Trials finding no differences in outcomes			
Searle NR	1997	Cardiac surgery	None
Kress JP	2000	Medical ICU	None
Huey-Ling L	2008	Cardiac surgery	None
Trials finding better outcomes with the benzodiazepine			
None			
Benzodiazepines vs. remifentanil			
Trials finding better outcomes with remifentanil			
Breen D	2005	Mixed ICU	Shorter duration of mechanical ventilation
Muellejans B	2006	Cardiac surgery	Earlier extubation and ICU discharge
Rozendaal FW	2009	Mixed ICU	Lighter sedation, shorter weaning time
Trials finding no differences in outcomes			
None			
Trials finding better outcomes with the benzodiazepine			
None			
Benzodiazepines vs. dexmedetomidine			
Trials finding better outcomes with dexmedetomidine			
Pandharipande PP	2007	Mixed ICU	More accurate sedation, more delirium/coma-free days
Riker RR	2009	Mixed ICU	Lower prevalence of delirium, earlier extubation
Ruokonen E	2009	Mixed ICU	Shorter duration of mechanical ventilation[a]

(continued)

Table 27.2 (continued)

First author	Year	Population	Outcome(s) improved
Maldonado JR	2009	Cardiac surgery	Lower incidence and duration of delirium
Esmaoglu A	2009	Eclampsia	Shorter ICU length of stay
Dasta JF	2010	Mixed ICU	Lower ICU costs
Jakob SM	2012	General ICU	Lighter sedation, fewer ventilation days
Trials finding no differences in outcomes			
None			
Trials finding better outcomes with the benzodiazepine			
None			

From Ely et al. [35]. Reprinted with permission from Elsevier Limited
Abbreviations: *ICU* intensive care unit
[a]According to post-hoc analysis adjusting for study center, sedative agent before randomization, and target sedation level

to recommend non-benzodiazepines for sedation in the ICU, but questions remain regarding which drug(s) should be preferred. Dexmedetomidine has the benefit of facilitating light sedation and reducing delirium risk [16, 17], but costs remain high and the patient population that benefits the most from this agent has not yet been clearly defined. Propofol is less expensive than dexmedetomidine and less prone to cause oversedation than benzodiazepines but its use in some patients is limited by hemodynamic effects. Other drugs, including opioids, clonidine, haloperidol, and atypical antipsychotics are sometimes used to manage agitation in the ICU, but evidence of benefit in randomized trials is needed before use of these agents can be widely recommended.

Spontaneous Awakening Trials (SATs)

Protocolized daily SATs (also known as daily interruption of sedatives), which were used in this case, were shown in two randomized controlled trials [12, 13] to improve outcomes, including long-term survival, but these trials were conducted at a time when heavy sedation was common so controversy exists regarding whether SATs are beneficial in ICUs that target light sedation. A recent multicenter randomized trial [19] sought to address this question by comparing a light sedation protocol alone vs. the light sedation protocol plus SATs and found no difference in outcomes. This trial, however, did not use a safety screen to identify patients likely to tolerate an SAT, and significantly higher sedative doses were delivered to patients in the SAT group. Whereas many ICUs continue to employ SATs and others do not, one thing is clear—SATs are most beneficial when they result in an overall reduction of sedative exposure.

Sedative-Related Delirium

Delirium can be caused by a variety of insults (e.g., both respiratory failure and sedatives were implicated in this case), but most studies to date showing that delirium is associated with adverse outcomes—including delayed extubation, prolonged hospitalization, increase mortality, and long-term cognitive impairment (see Delirium and Long-Term Outcomes section)—have not distinguished one type of delirium from another. Thus, it is not known if certain phenotypes of delirium are more injurious (or benign) than others. Sedative-related delirium has recently received attention because one study [20] found that patients whose delirium resolved within 2 h of sedative discontinuation (so called rapidly reversible, sedation-related delirium) had better outcomes than those whose delirium did not resolve quickly. More data on the effects of sedative-related delirium are needed before it can be concluded that this form of delirium is not harmful given that this study's results were

based on a very small number (N = 12) of patients who had rapidly reversible, sedation-related delirium.

Prevention of Delirium

Critically ill patients often develop delirium early during the course of their illness, so prevention of delirium in the ICU is a major challenge. In light of evidence from the geriatrics literature [21] suggesting that non-pharmacological prevention strategies, such as frequent orientation, sleep protocols, and early mobilization, are effective in some settings, similar strategies have been recommended in the ICU. One study, for example, found that ICU patients using earplugs to promote sleep had less confusion than those without earplugs [22], and another found that mechanically ventilated ICU patients managed with early physical and occupational therapy spent fewer days delirious than those in the control group [23]. No randomized trial to date, however, has examined whether a multicomponent prevention protocol, widely considered beneficial outside the ICU, can prevent delirium in the ICU. Though the risk of implementing such protocols is likely low, the cost may be high so evidence is needed to guide use of prevention protocols.

Antipsychotics

Though not used in the current case, antipsychotics (whether the typical agent, haloperidol, or any one of a number of atypical antipsychotics) are frequently used to treat delirium in the ICU despite a lack of evidence from randomized trials. Two placebo-controlled, randomized trials [24, 25] have now reported that haloperidol was no better than placebo in reducing delirium in the ICU, and one of these also found no benefit with ziprasidone, an atypical antipsychotic [24]. One small trial (N = 36) did suggest that quetiapine hastened resolution of delirium compared with placebo [26], but neither atypical nor typical antipsychotics were recommended in the recent SCCM guidelines [4] given the need for more evidence and the association between these drugs and adverse events in other settings. If used to treat delirium in the ICU, clinicians should consider discontinuing antipsychotics prior to ICU discharge to reduce the likelihood that patients will be unnecessarily discharged from the hospital with a new prescription for one of these medications [27].

Delirium and Long-Term Outcomes

Several observational studies have examined the relationship between delirium in the ICU and long-term outcomes in survivors of critical illness. Initially these studies focused on long-term mortality, finding that (compared with non-delirious patients) those with delirium in the ICU are more likely to die in the months to years after critical illness [28–30]. Though one recent negative study [31] generated some controversy regarding the relationship between delirium and mortality, studies examining delirium as a predictor of long-term cognitive impairment have been consistent—patients with delirium, especially over a prolonged period of time, are at highest risk for long-term cognitive impairment after critical illness [32–34], a poor outcome that is now recognized to affect up the one-third of survivors. It remains unclear whether delirium itself is injurious or is a marker of underlying brain injury, and the mechanisms of brain injury leading to delirium and long-term cognitive impairment have yet to be firmly elucidated. The answers to these questions are critically important given that the most effective prevention and treatment strategies are likely to be those directed at the mechanisms of injury.

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