Chapter 14

Sedation, Analgesia Delirium in the ECMO Patient

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Additional information is available at the end of the chapter

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Abstract

The goal of this chapter is to identify medications frequently utilized for sedation and analgesia in Extracorporeal Membrane Oxygenation (ECMO) patients. In addition to describing basic pharmacologic principles of these medications, we discuss their benefits and disadvantages and explain the effects the ECMO circuitry will have on pharmacokinetics of each drug. We also discuss need for various depths of sedation and the utility of neuromuscular blocking agents. Emerging techniques for achieving appropriate sedation will be identified. An explosion of literature in recent years has led to Intensive Care Unit (ICU) delirium increasingly being recognized as an indicator of poor outcomes in the general ICU population. We discuss strategies to manage this complex and multifactorial issues, and how they can be applied to our particular subpopulation of ECMO patients.

Keywords: sedation, analgesia, agitation, delirium, neuromuscular blocking agents, ECMO sequestration

1. Introduction

The basic principles of initiation and titration of sedatives and analgesics in the critically ill apply to those on Extracorporeal Membrane Oxygenation (ECMO). There are, however, some unique characteristics that pertain to the patient as well as the ECMO device itself that may help guide the intensivist in this particular subset. We will describe the basic pharmacologic principles of commonly used medications for providing sedation and analgesia and nonpharmacologic interventions. Emerging techniques for achieving appropriate sedation will be identified that include ECMO in the awake patient.

The ECMO circuitry has its own unique effects on the pharmacokinetics of each drug. We will also discuss the need for various depths of sedation and the utility of neuromuscular blocking

agents. This chapter also includes a discussion of monitoring and identifying the emerging techniques for management of sedation, analgesia, and delirium that include ECMO in the awake patients.

The reader should be able to identify the most commonly used analgosedation practices in ECMO patients after reading this chapter as well as the emerging techniques. They should understand the effect of the ECMO circuitry on pharmacokinetics of each drug described. We also hope to increase the understanding of the complex issue of Intensive Care Unit (ICU) delirium. The authors hope the readers will use the information to develop a systematic approach for delivering and titrating targeted analgosedation as well as for identifying and managing delirium in the critically ill ECMO patient.

2. Sedation and analgesia

The American College of Critical Care Medicine task force recently revised its clinical practice guidelines for the management of pain, agitation, and delirium in critically ill adult patients [1]. These guidelines recognize that pain is common in Intensive Care Unit (ICU) patients and may lead to both acute and long-term sequelae. In the acute setting, pain increases the proinflammatory balance of cytokines and may contribute to tissue hypoperfusion due to arteriolar vasoconstriction [2,3]. Opiates decrease this stress response and decrease tissue metabolic oxygen consumption [2]. Later, acute pain may lead to PTSD and Chronic Pain in patients who survive their critical illness [4,5]. Sedatives such as benzodiazepines may be used to decrease the stress response; however, they may have negative consequences that could worsen outcomes in ICU patients [1]. The 2013 guidelines thus advocate for pain assessment in ICU patients and an "analgesia-first" approach to sedation [1]. For patients undergoing ECMO, many considerations are similar to those encountered in other critically ill populations; however, certain factors will require additional consideration in this vulnerable group. Ultimately, the choice of medication for sedation and analgesia in a patient on ECMO will rely on multiple pharmacokinetic and pharmacodynamics considerations, clinical circumstances, patient's variables, and the goals of the team managing the patient [6].

Although intravenous opioids have been a mainstay of ICU analgesia for many years, much of the pharmacokinetic data comes from single-dose studies in healthy volunteers [7,8]. ECMO further complicates the situation by altering the pharmacokinetics of analgesics and sedatives [9,10]. The depth and duration of sedation as well as the titratability of the medication(s) selected must be considered. Often the level of sedation tolerated will depend on the patient's stability and sedation goals may vary considerably over time. This is especially true during the initial period after initiation of ECMO. At this stage, greater levels of sedation and sometimes chemical paralysis may be required. At the same time, the patient is frequently still in a state of hemodynamic or metabolic shock. Patients with an open chest due to central cannulation and those who require multiple painful procedures will require a greater degree of sedation to decrease movement and the consequent risk of cannula dislodgement. Medication interactions with the ECMO circuit itself must also be taken into account. Circuit seques-

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tration of highly lipophilic medications will decrease their bioavailability. This issue will be discussed in more detail in a later part of this chapter. Renal and hepatic functions are often impaired in patients requiring ECMO [11]; thus, the half-life of many medications can be prolonged; metabolites and compounding agents such as propylene glycol may accumulate leading to unwanted side-effects.

Route of administration is another concern with critically ill patients on ECMO. Enteral administration is cheaper and decreases reliance on parenteral access but may result in erratic and unpredictable absorption [6]. Submucosal and IM administration is generally unreliable in patients suffering from shock [8]. The 2013 Clinical Practice Guidelines from the Society of Critical Care Medicine consequently recommend intravenous opioids as the first-line drug class of choice to treat nonneuropathic pain in critically ill patients [1]. Intravenous administration provides faster onset, higher bioavailability, and rapid titratability [8]. This proves advantageous when administering medication prior to an invasive procedure or when following a sedation protocol. As the patient progresses in their course, lesser levels of sedation and analgesia may be required and minimal analgesia and sedation may be necessary [12]. At this point, continuous infusions may be discontinued and intermittent dosing of analgesics may prove sufficient.

All the available IV opioids can be titrated to achieve equally effective levels of analgesia [1]; thus the main difference between opiates comes down to cost, pharmacokinetic properties, and pharmacodynamic distinctions [6]. Opioids with agonist-antagonist properties should be avoided in critically ill patients in general due to decreased analgesic efficacy and the potential for triggering withdrawal in opiate dependent patients [6]. Meperidine is an undesirable choice because of potential drug interactions with serotonergic and dopaminergic agents, vagolytic side effects and the buildup of normeperidine, a metabolite which lowers the seizure threshold [8]. Fentanyl, a synthetic opioid with a rapid onset and short distribution half-life, is one of the most commonly used opioids in the ICU [13]; however, because fentanyl and its derivatives, sufentanil, alfentanil, and remifentanil, are highly lipophilic, they are extensively consumed by the ECMO circuit [10]. It has been demonstrated that within hours of administration, nearly the entire dose of fentanyl is lost in an ex vivo ECMO circuit primed with blood [14,15]. With such rapid absorption rates, exceedingly high doses of fentanyl would be required to maintain the desired level of analgesia. Furthermore, a patient previously exposed to high doses of opiates may experience withdrawal if placed on ECMO while already receiving fentanyl analgesia. Fentanyl may thus best play the role of a rapid onset analgesic used for brief but painful procedures.

From a pharmacokinetic standpoint morphine may be the preferred analgesic during ECMO. Because it is hydrophilic, it shows little absorption into the ECMO circuit [14,15]. Morphine was in fact considered the "preferred analgesic agent for critically ill patients" by the older 1995 guidelines for analgesia and sedation published by the Society of Critical Care Medicine [16]. Some of morphine's attributes however make it less desirable for use in the critically ill population. Histamine release from morphine may contribute to bronchospasm and hypotension [6]. In renal failure, accumulation of the active metabolite morphine-6-glucuronide may lead to prolonged sedation. Hydromorphone, a semisynthetic opiate, may thus prove a more

suitable option for IV analgesia in patients on ECMO. Although there is no specific study of hydromorphone's pharmacokinetics in an ECMO circuit, the drug's hydrophilic nature should keep sequestration at acceptable levels. There is no histamine release associated with large doses of hydromorphone, and although the parent drug may accumulate in renal and hepatic impairment, there are no active metabolites. The half-life of hydromorphone is 2–3 h, allowing for either intermittent bolus dosing or a continuous infusion to maintain the desired level of analgesia. Oxycodone, another semisynthetic opioid, may be given enterally for patients who are expected to have adequate absorption from their gastrointestinal tract. It is metabolized by the cytochrome P450 system, thus the dose should be reduced in hepatic dysfunction. Peak effect is reached after approximately 30 minutes to an hour and the duration of its effect is approximately 3–6 h. Oxycodone is relatively hydrophilic and so should not significantly bind to the ECMO circuit.

Analgesic adjuncts such as intravenous (IV) acetaminophen, gabapentin, ketamine, and dexmedetomidine may be used to decrease reliance on opioid analgesics and minimize their side effects. Unfortunately, many of these medications have only been studied on a limited basis in the ICU population, and data for patients receiving ECMO is remarkably limited. IV acetaminophen has been approved by the US Food and Drug Administration (FDA) for use along with opioids for pain management after major and cardiac surgery [17,18]. However, it has not been studied for extended periods of time or in a population with a high incidence of organ failure such as ECMO patients [19]. Additionally, the benefits of acetaminophen may not be as apparent or relevant in a population that requires long-term ICU level care. Neuropathic pain in settings such as burns, neuralgia, and neuropathy tends to be poorly treated by opioids [1]; however, it may respond to medications such as gabapentin and pregabalin that target calcium channels in the central nervous system [6,20]. If patients have been started on these medications due to pre-existing conditions, continuation of the therapy is prudent to avoid withdrawal. Unfortunately, pharmacokinetics can be complicated by unpredictable absorption from the GI tract, renal dysfunction, renal replacement therapy, and uncertain interactions with the ECMO circuit.

Since ECMO is frequently complicated by hemodynamic instability and rapidly escalating requirements for sedation and analgesia [9], ketamine infusions have been used to optimize patient comfort without increasing the depth of sedation or contributing to hypotension. Ketamine is an NMDA antagonist that has been shown to augment opiate analgesia without decreasing sympathetic tone [21]. Limited data exists on long-term ketamine use in critically ill patients; however, some trials have shown decreased opiate usage, improved gastrointestinal motility, and decreased vasopressor requirements in patients treated with ketamine [22]. Similarly, a retrospective review of ketamine in 26 ECMO patients treated at a single center demonstrated a decrease in vasopressor requirements and a decrease in sedation requirements while maintaining the same level of sedation [23]. The doses of ketamine used in the ECMO trial (50–150 mg/H) were substantially higher than those described for analgesia in other studies. Since ketamine is lipophilic, this may be attributable to circuit sequestration of ketamine. A possible concern with ketamine analgesia in patients, who have cardiogenic shock,

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is that the increase in blood pressure may come at the expense of a decrease in cardiac output and an increase in systemic and pulmonary vascular resistance [24].

When an analgesia-based regimen is insufficient to provide adequate patient comfort, or a greater depth of sedation is required due to clinical circumstances, a sedative may be initiated. Just as opiates have been the mainstay of analgesia in the ICU, benzodiazepines have traditionally been used for sedation in critically ill patients. Benzodiazepines activate -aminobutyric acid A receptors in the central nervous system leading to anxiolysis, amnesia, sedation, and an increase in the seizure threshold [8]. Recent evidence however has identified these agents as a leading, modifiable cause of delirium in hospitalized patients and implicated them in prolonging the duration of mechanical ventilation and ICU stays [25–27]. Other agents such as propofol and dexmedetomidine have shown superiority in comparison to benzodiazepines by reducing ICU stays and duration of delirium [26–28].

Of the benzodiazepines, midazolam is frequently used as an infusion for short to intermediate duration sedation of ICU patients [8]. It is water soluble, has a rapid onset of action, and a relatively shorter half-life of 2–5 h. However, with prolonged infusion, midazolam and its active metabolite 1-hydroxymidazolam glucuronide may accumulate, contributing to prolonged sedation and respiratory depression. Liver and renal failure may both prolong this effect. Lorazepam is metabolized by glucuronidation in the liver to an inactive metabolite and is thus less affected by renal and hepatic dysfunction. Since it has a longer half-life of 10–20 h, it may be given as an infusion or bolused on an as needed basis. Midazolam is highly lipophilic and is to a large extent absorbed by the ECMO circuit. In one study 50% of midazolam remained available after 30 min of in vitro ECMO circulation, and only 13% was detected after 24 h [29]. On the other hand, another study evaluated lorazepam and showed that 70% of lorazepam remained at 24 h [61]. Since lorazepam is somewhat less lipophilic, a lesser degree of sequestration would be anticipated.

Of the nonbenzodiazepine sedatives, propofol is extensively absorbed by the ECMO circuit [30]. This property and its tendency to cause hypotension would make propofol a less desirable agent for the sedation of patients on ECMO. Dexmedetomidine, a selective alpha-2 receptor agonist, with sedative and analgesic properties, has demonstrated substantial advantages over benzodiazepines in the care of critically ill patients. Patients sedated with dexmedetomidine are more easily aroused, have a reduced incidence of delirium, decreased sympathetic tone, and less respiratory depression [1,28]. A recent study showed that addition of dexmedetomidine to standard care of agitated, mechanically ventilated patients resulted in more rapid resolution of delirium and more ventilator free days [31]. Dexmedetomidine may not be appropriate in patients requiring a deep level of sedation or those with hypotension or bradycardia [6]. Dosage adjustments will likely be required for patients on ECMO due to significant interactions with the PVC tubing of the circuit [32].

Monitoring levels of sedation and analgesia is crucial in decreasing the likelihood of undesired outcomes [1]. Chanques et al. demonstrated that a protocol for systematically assessing and treating pain and agitation in critically ill patients not only decreased pain and agitation but also decreased the duration of mechanical ventilation and the incidence of nosocomial infections in a mixed medical-surgical population [33]. Although a patient's self-assessment

of pain is considered the "gold standard" for pain assessment, this is frequently difficult to obtain in the ICU setting. Hemodynamic indicators of pain are not validated or reliable [1]. Behavioral scales have been developed as an objective tool for measuring pain in patients unable to communicate. Two scales in particular, the Behavioral Pain Scale and the Critical Care Pain Observation Tool have been found to be both reliable and valid in patients who are unable to report pain but have intact motor function [34]. Although further validation and study is warranted, implementation of these scales has been shown to be feasible and to lead to improved pain management and clinical outcomes [33,35,36]. Whether such protocols of pain assessment and titration would improve outcomes in ECMO patients remains to be seen.

With regard to sedation, the Richmond Agitation-Sedation Scale (RASS) and the Sedation-Agitation Scale (SAS) are considered the most valid and reliable sedation assessment tools for measuring depth of sedation. They demonstrate high inter-rater reliability as well as convergent and discriminant validation in a relatively high number of subjects [1]. The RASS additionally provides a goal for the titration of sedation. In patients who are chemically paralyzed, as ECMO patients may be immediately after cannulation, one of several objective sedation monitors, such as the bispectral index (BIS), Narcotrend Index, Patients State Index or state entropy, should be used [1]. Electroencephalogram monitoring should be used in patients suspected of having nonconvulsive seizures.

3. Neuromuscular blockade and ECMO/ARDS

Neuromuscular blocking agents (NMBAs) have been controversial with regard to their efficacy in treating acute respiratory distress syndrome (ARDS) (we will not discuss the use of NMBAs for the initial intubation of the patient). Due to lack of evidence on a large scale, no clear recommendations exist regarding the use of NMBAs in ARDS. Early work suggested that anesthesia and paralysis cause a ventilation/perfusion mismatch and impair gas exchange [37]. The traditional view on NMBA use in the critical care setting is largely negative, with a number of potential complications associated with this therapeutic modality [38,39]. However, other work over the past 12 years has indicated that use of NMBAs in acute respiratory distress syndrome (ARDS) has been shown to improve oxygenation and decrease mortality in most hypoxemic patients [40]. What is applicable in ARDS is also applicable in ECMO because ECMO is just a further device extension beyond ventilators and high-frequency oscillators [41,42].

Gannier et al. asserted that the hypoxemia in ARDS reaches its worst levels in the first 48 h. In a study of 56 patients with ARDS, improved oxygenation was seen in patients randomized to NMBAs in the first 48 h while receiving volume assist control with a tidal volume of 6–8 ml/kg [43]. Another similar study reported that early NMBA use may contribute to modulation of the pro-inflammatory response [44]. Additionally, a third study of 340 patients where *cis*-atracurium was administered in the first 48 h of development of ARDS found that the NMBAs improved the adjusted 90-day survival and increased time off of the ventilator without increasing muscle weakness [45].

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Two recent meta-analyses based on randomized control trials analyzed the use of NMBAs in ARDS. Neto et al. performed a systematic review of the literature and meta-analysis of studies conducted between 1966 and 2012, and the three abovementioned studies were the only acceptable, high-quality trials performed [46]. The authors concluded, based on these three studies, that that the use of NMBAs in the early stages of ARDS leads to an improved outcome. Alhazzani et al., in a second meta-analysis, demonstrated a decreased mortality rate at 28 days among those receiving NMBAs in early ARDS [47]. They stated that nine patients need to be treated to save one life. They also found that there was a reduced risk of barotrauma and an increased number of days without mechanical ventilation during the first four weeks in those receiving NMBAs. Furthermore, they showed that the PaO2:FiO2 ratio was improved at one, two, and three days.

Physicians must be aware of the potentially important pathophysiological events that can occur with the use of NMBAs in hypoxemic patients [40]. These include increases in thoracopulmonary compliance, functional residual capacity, perfusion of ventilated spaces, and recruitment of portions of the lung that have little compliance. There can be decreases in pulmonary shunt, muscular O_2 consumption, overdistention of high-compliance areas, derecruitment, end-expiratory collapse, asynchronous patient-ventilator dynamics, barotrauma, volutrauma, biotrauma, and atelectrauma. The debate continues as to the best ventilation practices/strategy in ARDS. The problem with NMBAs is that they seem to eliminate the opportunity for the use of spontaneous modes [40].

Additionally, every practicing intensivist must be aware of ICU-acquired weakness (ICUAW), a polyneuropathy and/or myopathy, that occur in 34–60% of the patients with ARDS [48–50]. It was associated with independent risk factors such as organ dysfunction, female gender, length of time on a ventilator, and corticosteroid administration [51], and there is some evidence it is related to hypothermia, hyperglycemia, ICU length of stay, low albumin, and vasopressors [52–54]. While NMBAs have historically been associated with ICUAW, recent evidence contradicts this view, at least with nonsteroidal NMBAs [40].

It is of great importance to use a nerve stimulator for the monitoring of neuromuscular blockade [55]. If the dose of NMBAs is limited, there may be a decrease in the subsequent risks of ICUAW and complications from residual neuromuscular blockade [56]. Peripheral nerve stimulator use is mandatory in order to facilitate appropriate titration of NMBAs. Train of four (TOF) monitoring is the primary method for assessment of NMBA and generally involves the use of supramaximal electrical impulses every 0.5 s applied to the ulnar, facial, or posterial tibial nerve with a resultant identifiable pattern or response [55]. Instruction in TOF monitoring is beyond the scope of this chapter.

Hraiech et al. make the observation that based on the available evidence provided by randomized control trials, NMBAs can be integrated safely into the concept of protective ventilation [40]. The use of NMBAs should be confined to the acute phase of ARDS. Spontaneous breathing must be encouraged when the severe phase has passed and in those with mild and moderate ARDS from the outset. Finally, never forget to sedate a patient in which a NMBA is used. In some countries, such as the USA, this can be a cause of legal action or discipline [57]. While the above suppositions related to NMBAs were not directly related to ECMO, the difficulty in

oxygenating an ECMO patient should at least lead to the consideration of pharmacologic paralysis.

4. Drug sequestration in ECMO

Drug therapy while a patient is on ECMO may be affected by multiple pharmacokinetic alterations, including volume of distribution and protein binding. One of the reasons a patient's volume of distribution may be increased is due to sequestration of drug within the ECMO circuit. Sequestration of drugs into the ECMO circuit is a well-known phenomenon with certain drug properties predicting which medications may bind to the ECMO circuit [15]. Medications that are considered lipophilic, such as propofol, will have a high octanol/water partition coefficient (log *P*) and will be soluble in organic materials such as PVC tubing [15]. Conversely, medications that are considered hydrophilic may be unaffected by the ECMO circuit. In an ex vivo study performed by Lemaitre and colleagues, the concentration of propofol decreased to 11% of expected values after 24 h in a closed ECMO circuit [30], while concentrations of vancomycin, a relatively hydrophilic drug, remained unchanged.

In addition to lipophilicity, the degree of a drug's protein binding may affect sequestration in the ECMO circuit. Shekar and colleagues performed an ex vivo study and determined that drugs with significantly reduced concentrations at 24 h were either highly protein bound (>80%), highly lipophilic (log $P > 2.3$), or both [60]. For medications with the similar lipophilicity, the degree of drug recovery was based on protein binding. Both ciprofloxacin and thiopentone have similar lipophilicity (log *P* 2.3; however, greater reductions were seen in the drug with higher protein binding, thiopentone (88%), compared with ciprofloxacin (4%). This held true when comparing two hydrophilic drugs vancomycin and ceftriaxone. Circuit drug recovery at 24 h was higher for vancomycin (91%) compared with ceftriaxone (80%), which is more highly protein bound. It is unclear of why highly protein bound drugs bind to the ECMO circuit. It is postulated that proteins in the priming solution or in the patient's blood bind to the circuit and then the drug in turn binds to the protein sequestered in the circuit. Drugs that are both lipophilic and highly protein bound may be more prone to sequestration in the circuit. As an example, fentanyl a highly protein bound and lipophilic drug has been studied in ECMO with extreme reductions in concentrations (97%) at 24 h [14]. However, it is still unclear if the presence of both properties results in additive binding within the circuit.

In addition to considering drug properties to predict sequestration, it is imperative to evaluate the ECMO circuit components and their materials. Wildschut and colleagues showed significant differences in drug recovery for both fentanyl and midazolam in neonatal centrifugal pumps compared to neonatal roller pumps [15]. The neonatal centrifugal pumps had nearly one hundred fold increases in drug recovery for fentanyl and midazolam compared with the roller pumps, which may be due to the fact that roller pumps require more PVC tubing, potentially increasing the amount of drug-binding sites. The PVC tubing and membrane oxygenators used in ECMO have both been shown to sequester drug within the ECMO circuit; however, the PVC tubing is presumed to be responsible for the removal of a vast majority of

the drugs [61,62]. It is unclear if saturation of drug-binding sites on the PVC tubing occurs, as studies comparing drug recovery in new and used ECMO circuits show variable results [15,32,61]. The limitation of all of these studies is the short duration (<48 h) of drug exposure to the ECMO circuit. As ECMO has been used clinically for much longer periods of time, it is unclear if or when saturation of the ECMO circuit occurs and how this may impact drug therapy.

Once a patient is placed on the ECMO, drug sequestration is just one of the factors that can cause pharmacokinetic changes. Data for sequestration of drugs in the ECMO circuits are limited, and it is important to understand the majority of the data is derived from ex vivo experiments. When caring for a patient on the ECMO, it is imperative to consider the drug properties, type, and duration of ECMO, and patient's factors that influence drug dosing in order to prevent harm and/or therapeutic failure.

5. Delirium

Often used interchangeably with the term "acute brain dysfunction," delirium has consistently been shown to be an independent predictor of poor short-term outcomes in the critically ill. This includes increased mortality in mechanically ventilated patients as well as prolonged hospital and ICU stays [63,64]. There is now increasing evidence of delirium's ill effects in the long term as well. Long-term cognitive impairment has been linked to the development and duration of delirium in the ICU setting [65].

Delirium is defined as a disturbance in attention and awareness which is an acute change from baseline. Typically, it develops over a short period of time (over hours to days) and fluctuates throughout the course of the day. Patients often present with additional disturbances in cognition (e.g., memory deficit, disorientation, language, visuospatial ability, or perception) [66,67].

There are three subtypes of delirium that are based on the patient's level of alertness: "hyperactive," "hypoactive," and "mixed." Often hypoactive delirium goes unrecognized and has been linked to poorer outcomes [68].

Patients on the ECMO are particularly vulnerable to the development of delirium given their severity of illness and comorbidities. Four independent risk factors for transition to delirium have been identified: pre-existing dementia, history of hypertension, and/or alcoholism, and a high severity of illness at admission [6]. However, there are many other factors that have been associated with this form of acute brain dysfunction—these can be further stratified based on (1) illness (2) patient's factors, and (3) environmental or iatrogenic factors [69] **(Table 1)**.

Care of the delirious patient in the ICU should focus on a three-step approach of monitoring, preventing, and treating delirium. At this time, there is limited data on delirium in the ECMO patients. Further research is essential in determining an evidence-based algorithm in the ECMO patient as there are many unique patient- and equipment-related factors specific to these patients that need to be investigated. The Confusion Assessment Method for the

Intensive Care Unit (CAM-ICU) is the most frequently applied screening and monitoring tool in the ICU setting (**Figure 1**) [70]. Proper assessment will guide further interventions.

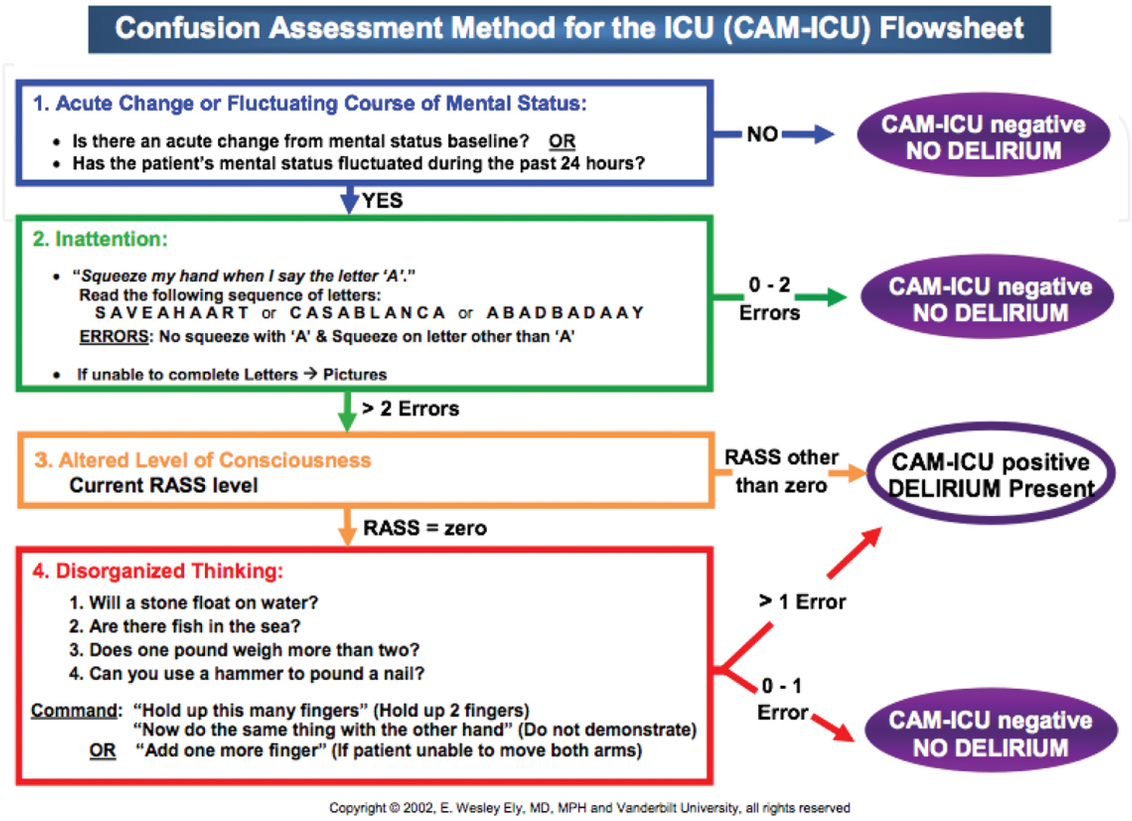

Figure 1. Confusion assessment method for the ICU (CAM-ICU) Flow sheet.

Illness	Patient's factors	Environmental/iatrogenic factors
Cardiovascular instability	Cognitive impairment, pre-existing dementia, and depression	Diagnostic procedures and therapeutic interventions
Acid base disorders	Age > 65	Use of restraints
Electrolyte abnormalities		Sensory deprivation: need for hearing aids and glasses
Sepsis		Sleep deprivation
Respiratory distress		
Acute CNS abnormalities		
http://www.mc.vanderbilt.edu/icudelirium/terminology.html		

Table 1. Factors that have been associated with delirium.

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Primary prevention should focus on decreasing the risk factors and minimizing iatrogenic causes known to increase the likelihood of transition to delirium. Management for both prevention and treatment can be further subcategorized into nonpharmacologic and pharmacologic interventions. These include minimizing loud noises and interruptions, a nonpharmacologic sleep protocol, stimulation during the day, and frequent reorientation to person, place, and time. Pharmacologic prevention of delirium has not been shown to decrease the likelihood of its occurrence [6]. The authors believe this practice may actually lead to over sedation and increase the likelihood of transition to delirium and do not recommend this approach based on existing evidence at this time. Daily assessment of analgesia and sedation requirements and deliberate choices in agents are an important part of the management (**Figure 2**).

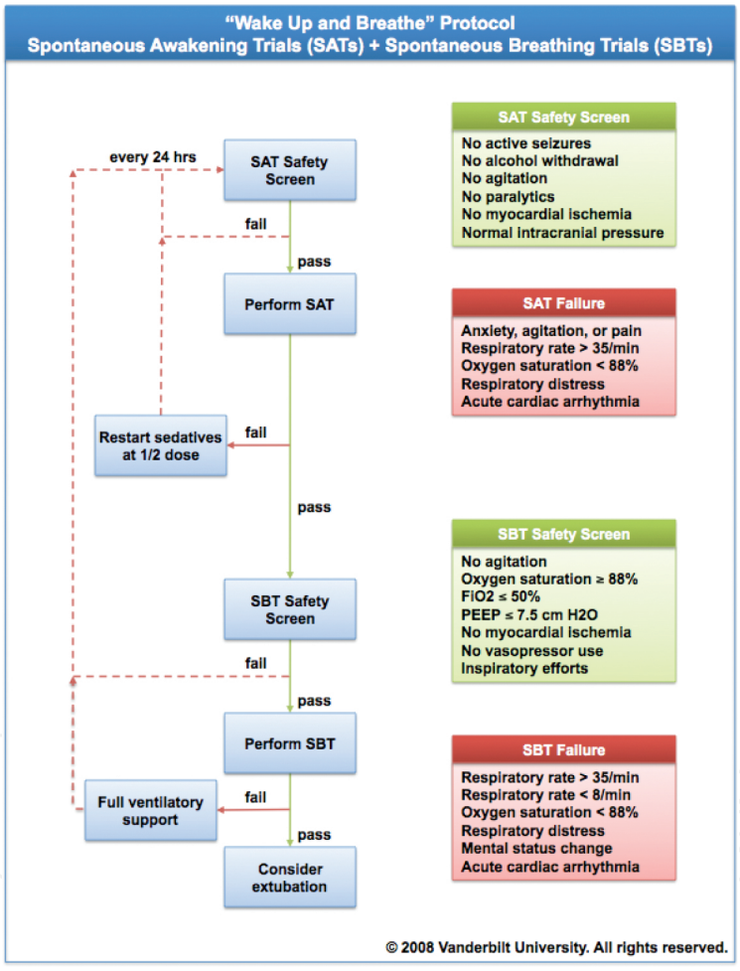

Figure 2. 'Wake up and breathe' protocol.

Benzodiazepines have been proven in multiple ICU settings to increase the likelihood of transition to delirium [71, 72]. Traditionally, they have been used for deep sedation in the ECMO patients because of their relative preservation of hemodynamic stability and unique pharmacologic property of lorazepam that would ensure adequate plasma concentrations in patients on the ECMO. In the future, the use of deep sedation with medications that remain in

the system long after titrating off may lead to this practice being called into question. Deep sedation may be provided with multiple other sedatives that were discussed in the section regarding sedation and analgesia.

As further evidence emerges, prevention and treatment of delirium in the ECMO patient will become more standardized. Early mobilization and liberation from mechanical ventilation should be included in goals for prevention and management of delirium in the ECMO patient. There is compelling evidence that protocol-based treatment with these goals in mind can improve clinical outcomes in the general ICU population [73].

In keeping with the goal of early liberation of mechanical ventilation, many centers are exploring strategies for the use of ECMO in the awake patient. This may decrease the morbidity and mortality associated with mechanical ventilation, deep sedation, and immobility that have traditionally accompanied the use of ECMO. Additionally, it is possible for patients to breathe spontaneously, which might prevent respiratory muscle atrophy. While this has been best documented in the pediatric population and adult VV-ECMO patients being bridged to lung transplantation, this could also be utilized in the VA-ECMO patient. In such a case, close monitoring would be essential to ensure that the patient's breathing pattern and neurologic status are not compromising the patient's hemodynamics and respiratory status [74–76].

6. Conclusion

Increasingly, complications related to sedation, analgesia, and delirium are being recognized as factors that may play a role in morbidity of the critically patient. The decision to initiate medications for sedation, pain control, or agitation should be made by a clinician with intimate knowledge of the most commonly used agents. The use of deep sedation, light sedation, or minimal sedation should be decided upon based on the clinical picture specific to each individual patient on VA or VV ECMO. Pain must be accurately assessed in patients who may or may not be able to verbally express pain scores and titrated to response. The initiation of medications for agitation or anxiety must be decided upon with careful consideration in this critically ill population and the need for these medications should be reviewed on a daily basis.

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