HHS Public Access

Author manuscript

Curr Opin Crit Care. Author manuscript; available in PMC 2020 June 01.

Published in final edited form as:

Curr Opin Crit Care. 2019 June ; 25(3): 218–225. doi:10.1097/MCC.0000000000000615.

In the ICU – Delirium Post Cardiac Arrest

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Abstract

Purpose of review: This review aims to describe the clinical impact and assessment tools capable of identifying delirium in cardiac arrest survivors as well as providing strategies aimed at preventing and treating delirium.

Recent findings: Patient factors leading to a cardiac arrest, initial resuscitation efforts, and post-resuscitation management all influence the potential for recovery as well as the risk for development of delirium. Data suggests that delirium in cardiac arrest survivors is an independent risk factor for morbidity and mortality. Recognizing delirium in post-cardiac arrest patients can be challenging, however, detection is not only achievable, but important as it may aid in predicting adverse outcomes. Serial neurologic examinations and delirium assessments, targeting light sedation when possible, limiting psychoactive medications, and initiating patient care bundles are important care aspects for not only allowing early identification of primary and secondary brain injury, but in improving patient morbidity and mortality.

Summary: Developing delirium after cardiac arrest is associated with increased morbidity and mortality. The importance of addressing modifiable risk factors, recognizing symptoms early, and initiating coordinated treatment strategies can help to improve outcomes within this high risk population.

Keywords

delirium; neurologic injury; cardiac arrest

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Conflict of Interest: none

Introduction

Cardiac arrest is the most common cause of hypoxic-ischemic brain injury,[1,2] with neurologic injury accounting for the majority of post-resuscitation morbidity and mortality.[3,4] Outcomes of cardiac arrest survivors are dependent on the effectiveness of immediate resuscitation, transfer, and post-resuscitation management in the ICU.[1] Delirium, a syndrome of acute brain injury, has been described in critically ill patients for decades, including in patients who suffer from cardiac arrest. The first mention of delirium in cardiac arrest survivors described “organic brain syndrome” as a constellation of symptoms including disorientation, disorganized thinking, restlessness, or agitation.[5] Evolving nomenclature and diagnostic criteria have since been instituted that better characterize delirium as a syndrome of acute brain dysfunction, unifying its description across multiple specialties.

Delirium has already been recognized as an ubiquitous problem affecting up to 80 % of medical and surgical intensive care unit (ICU) patients.[6–9] Recognition and diagnosis are important to aid in early interventions as increasing duration of delirium is associated with prolonged time on mechanical ventilation, longer ICU and hospital stays, greater long-term disability, and worse cognitive dysfunction.[10–13] Of growing interest is the prevalence and impact of delirium within post-cardiac arrest patients. Are they affected at the same rate? In the same way? And by the same adverse outcomes? These questions are important in guiding clinicians to target optimal prevention and treatment strategies focused on improving outcomes within this clinically challenging group of patients. Unfortunately, patients who suffer from cardiac arrest and anoxic brain injury are often excluded from studies of delirium, but data suggest delirium in cardiac arrest survivors is an independent risk factor for morbidity and mortality.[14] This chapter will review the definition of delirium in critically ill patients, discuss risk factors associated with delirium, and provide the basis for clinicians to develop strategies aimed at preventing and treating delirium in the post-cardiac arrest patient.

Definition of Delirium and Motoric Subtypes

Delirium is a syndrome that develops over a short period of time and includes a disturbance of consciousness, inattention, and a change in cognition. It can be a direct result of a general medical condition, substance, medication, or a combination of causes.[15] It has been further differentiated according to the level of arousal and motor activity into three motoric subtypes: hyperactive, hypoactive, and mixed delirium.[16] Hypoactive delirium is characterized by a flat affect, withdrawal, apathy, or lethargy. The hyperactive subtype includes agitation, restlessness, emotional lability, or violence. Patients with mixed delirium experience periods of both hypoactive and hyperactive delirium. The distribution of subtypes across medical and surgical ICU patients shows the majority of patients experience hypoactive delirium, which is classically more difficult to identify and, therefore, largely under-reported.[16–18] It is unclear whether or not the predominance of hypoactive delirium persists in post-cardiac arrest patients as only two studies have described motoric subtypes within this subgroup with varying distributions.[19,20] Also unclear is whether patients with hypoactive delirium after cardiac arrest are at increased risk of death compared to their

hyperactive or mixed counterparts, as has been seen in other medical and surgical populations.[17,21]

Risk Factors

The post-cardiac arrest population is unique from other ICU patients due to the severity of the acute brain insult and, often, significant underlying comorbidities. Patient factors leading to a cardiac arrest, initial resuscitation efforts, and post-resuscitation management all influence the potential for recovery[1] as well as the risk for development of delirium. Risk factors for the development of delirium, broken down by these stages, are listed in Table 1. It is important to note while discussing risk factors for development of delirium in this population that cardiogenic shock, or cardiac arrest in itself, is a risk factor for delirium—with increased duration of arrest associated with longer duration of delirium following ROSC.[14,19,20] Although not shown at this time to be an independent risk factor, the incidence of delirium in receiving targeted temperature management (TTM) was found to be 100% in a cohort of greater than 100 patients surviving and awakening following cardiac arrest.[19] It is unclear how the extent of brain injury, sedation practices, temperature targets, paralytics, and other factors influenced this high prevalence, and it remains an exciting area for further research.

Potentially modifiable risk factors for the clinician include obtaining ROSC as quickly as possible with continuous and adequate cardiopulmonary resuscitation (CPR) and defibrillation when indicated, correction of hypoxia, metabolic and electrolyte disturbances, prevention of hyperthermia, and treatment of underlying infection.[22–24] In patients previously taking statin medications, continued use is recommended as discontinuation has been associated with increased delirium.[25,26] In patients who progress to surgery, cardiac surgery without cardiopulmonary bypass appears to confer an advantage in decreasing delirium in some studies,[27,28] but multiple other patient factors should be considered in deciding the best surgical approach for each patient.

Assessment Tools

Early diagnosis of delirium is important for prognostication and avoiding exacerbating iatrogenic factors that will lengthen its course. Recognizing delirium is difficult in post-cardiac arrest patients as differentiating between encephalopathy, primary neurologic injury, and delirium can be challenging.[29] Detection, however, is not only achievable among neurologically critically ill patients, but identification of delirious features may aid in predicting adverse outcomes for these patients.[30] Assessment should first include establishing level of arousal through use of the Ramsay Sedation Scale,[31] the Riker Sedation-Agitation Scale,32 or the Richmond Agitation-Sedation Scale (RASS).[33,34] Once level of arousal has been determined and the patient is deemed responsive to voice, the clinician can proceed with assessing for the presence of delirium using one of two validated instruments in the ICU setting: the Intensive Care Delirium Screening Checklist (ICDSC)[35] or the Confusion Assessment Method for the ICU (CAM-ICU).[36,37] Evaluation for delirium using the ICDSC involves scoring of symptom presence over the course of a nursing shift, including altered level of consciousness, inattention, disorientation, hallucinations/delusions,

psychomotor retardation/agitation, inappropriate speech or mood, sleep disturbances, and symptom fluctuations, each valued at one point. Patients scoring 4 or more points screen positive for delirium. The ICDSC has also been used to classify patients as having subsyndromal delirium if they have some signs of delirium but do not meet full criteria.[38] Evaluation using the CAM-ICU is performed at a point in time and assesses for both an acute change in mental status and inattention plus either disorganized thinking or altered level of consciousness (Figure 1). The CAM-ICU has also been developed into a valid and reliable delirium severity scale, termed the Confusion Assessment Method for the ICU-7.[39]

There has been question as to whether patients should be evaluated for delirium while receiving sedation. A small subset of patients will screen positive secondary to sedation-related delirium that rapidly clears following discontinuation of sedatives and may not carry the same long-term risks as more persistent delirium.[40,41] For this reason, sedation should be paused whenever feasible for evaluations. If this is not safely possible, delirium evaluations should be continued with sedation (as the patient is able to participate), as failing to diagnose and intervene early on delirium far outweighs the risk of over-diagnosing a small group of patients.[42]

Patient Management

Sedation

Patients suffering from a cardiac arrest will often arrive to the ICU intubated with or without sedation. Serial neurologic examinations are especially important for both treatment and prognostication. Changes in neurologic exam should trigger a clinical response in the form of early involvement of a consultation service (e.g., neurology), repeat imaging, electroencephalography (EEG) placement, or family discussion of goals of care given the high level of morbidity and mortality associated with neurologic injury in these patients.[43–45] General sedation practices associated with improved outcomes while on mechanical ventilation are the same across all ICUs: target lower sedation levels and perform daily pauses in sedation in conjunction with daily spontaneous ventilator weaning trials for appropriate patients.[46–48] The notion that these patients require deeper levels of sedation as a way to decrease cerebral metabolic rate and injury has not been shown[49] and is discouraged. Deeper sedation has not been associated with any benefit in neurologic outcomes and carries increased risks including prolonged ventilator support, pneumonia, delayed wakening, delayed mobility, increased delirium, and can confound neurologic prognostication.[50] Further, deep sedation has been associated with increased delirium and decreased survival.[51–54] These general sedation recommendations are modified for patients with severe neurologic injury when TTM is indicated for optimization of hypoxic-ischemic encephalopathy. These patients, with or without use of neuromuscular blockade, are not candidates for light sedation. Moderate sedation is recommended to prevent awareness and recall while avoiding adverse effects associated with deep sedation. To our knowledge there are no prospective studies looking at outcomes between moderately versus deeply sedated patients during targeted temperature management periods, but retrospective review has shown moderate sedation to be safe and feasible.[55] Processed EEG monitoring to guide

depth of sedation should be considered, especially in patients treated with neuromuscular blockade,[56,57] though the authors recognize its use during TTM has not been studied.

Given the lack of evidence within the distinct population of cardiac arrest survivors, outside of targeting light sedation whenever possible, there are no strong recommendations for or against specific sedation strategies. Limited data for patients treated with TTM have shown a potential protective effect of propofol administration during rewarming.[19] Benzodiazepines are commonly administered in the post-cardiac arrest population given the high incidence of hemodynamic instability and treatment of seizures in the sub-acute period. Although benzodiazepines are heavily implicated in both development and duration of delirium in critically ill medical and surgical populations,[58–62] these effects are not as strongly associated within this sub-group.[19] While this may be due to the lack of adequately powered studies (since most delirium studies exclude patients after cardiac arrest), it is also possible that this patient population is unique in their response to sedatives and other centrally active medications due to the extent of neurologic injury, degree of multi-organ dysfunction, drug metabolism, individual seizure risk, and subsequent cerebral hyper-metabolism associated with ROSC or rewarming after cooling. Although midazolam infusions appear to contribute to delayed awakening in patients following TTM,[63] patient outcomes including mortality and long-term neurologic function do not appear altered by its use.[64]

In studies excluding patients with active myocardial ischemia, dexmedetomidine (alpha-2 agonist) compared to benzodiazepine infusions showed that the former reduced the burden of brain dysfunction with the most notable adverse side effect being bradycardia.[65,66] This might be of particular concern in hypothermic patients who are already at increased risk for bradycardia but may benefit most from dexmedetomidine's potential neuroprotective effects.[67] There is further suggestion that for patients requiring surgical intervention, the use of prophylactic dexmedetomidine is preventative in the development of delirium.[68,69] The beneficial mechanism of dexmedetomidine is likely multifactorial and may include a decrease in administration of opioids due to analgesic and subsequent opioid-sparing properties, better quality of sleep, lack of anticholinergic effects, and its association with decreased inflammatory biomarkers.[69,70]

Within the ICU, patients commonly receive sedative or analgesic medications. In the non-critically ill patient population, both the number of medications administered22 and their psychoactive effects[71] have been suggestive of precipitating delirium. Hepatic and renal function has been found to be impaired in greater than 50% of post-cardiac arrest patients; pharmacokinetic alterations of administered medications can be profound.[72] Further, hypothermia—either targeted or unintentional—can increase plasma concentrations of commonly administered medications such as propofol by approximately 30%,[73] fentanyl by approximately 25%,[74] and midazolam by approximately 10% for each degree Celsius (C) decrease from core temperature of 36.5 degrees C.[75] Regardless of the use of targeted temperature management in these patients, continuous infusion of sedative and analgesic medications leads to accumulation and tolerance over time. Practices to reduce exposure to psychoactive medications are an important component of ICU care and strategies need to be employed to reduce the exposure in patients as early as possible.[47]

Prevention Strategies

There has been increasing evidence in critical care literature illustrating the benefit of patient care bundles in not only reducing the incidence of delirium, but decreasing mechanical ventilation use, coma, restraint use, and ICU readmissions while improving survival and post-ICU discharge disposition.[48] To optimize critical care management, the Society of Critical Care Medicine (SCCM) recommends the ABCDEF bundle be applied to all ICU patients, including those post-cardiac arrest, as part of their ICU Liberation initiative. Components of the ABCDEF bundle include: **A**ssessing and treating pain, **B**oth Awakening and Breathing Trials, **C**hoice of appropriate sedation, **D**elirium monitoring and management, **E**arly mobility and Exercise, and **F**amily Engagement.[76]

Indeed the best way to treat delirium is to prevent it from happening in the first place. There are currently no recommended prophylactic medications or pharmacologic protocols for the prevention of delirium, although there is suggestion that use of low-dose dexmedetomidine in elderly post-operative patients[69] or via nocturnal administration[77] may decrease incidence. Additionally, low-dose ketamine has recently been shown in a randomized placebo-controlled trail of medical and surgical ICU patients to decrease both delirium incidence and duration. Further studies are required before ketamine for delirium prophylaxis can be routinely recommended. Although statin use within the ICU has been shown to be associated with less delirium in prospective cohort studies,[25,26] randomized controlled trials comparing statins to placebo have not shown decreased risk of delirium.[78,79]

The strongest prevention practice under current guidelines remains early mobility. Initiation generally progresses from passive range of motion to active range of motion, exercise in bed, sitting, standing, and ambulation depending on patient's sedation level, neurologic function, and physical abilities. Early initiation of physical therapy, even when limited to once daily sessions coordinated with pauses in sedation, has been shown to decrease delirium, polypharmacy and hospital length of stay in addition to improving functional outcomes at discharge.[80–82] Recognizing that there are potential obstacles to participation in the immediate post-cardiac arrest patient, physicians and clinicians should be continually assessing patients for appropriateness and initiation of physical therapy at the earliest possible time.

Delirium Management

Once diagnosis of delirium is made, clinicians must attempt to identify and exclude all reversible causes. As mentioned previously, reversible causes include hypoxia, hypercarbia, hypoglycemia, metabolic derangements, infection, or continued shock. An empiric protocol based on current practice guidelines for all ICU patients is suggested in Figure 2. Institutional protocols may vary but should broadly align with recommendations from the SCCM.

Specifically regarding treatment strategies in the agitated, delirious patient, dexmedetomidine may be superior in management to benzodiazepines, propofol, and placebo, particularly when used for liberation of mechanical ventilation.[83,84] Antipsychotic

medications, either typical or atypical, have increasingly become utilized in management, particularly for hyperactive delirium. Although shown not to be effective in prevention of delirium,[85] there has been mixed evidence about the efficacy of antipsychotics in decreasing duration of symptoms in several small studies.[86,87] A recent large randomized placebo-controlled trial of typical and atypical antipsychotics versus placebo, however, found no effect in decreasing duration of delirium;[88], thus, evidence does not support the use of antipsychotics for the treatment of delirium. When these medications are used for control of agitated symptoms, they should be used with caution. Adverse reactions including dystonias, neuroleptic malignant syndrome, and extrapyramidal effects are all possible. Haloperidol use in the post-cardiac arrest patient should include daily monitoring of QT interval measurements as QT prolongation and arrhythmias deteriorating to torsades de pointes are known complications. Once initiated, clinicians should be mindful to create discontinuation strategies as antipsychotics initiated within the ICU are frequently inappropriately continued at hospital discharge and could pose long-term risks to patients.[89]

The treatment strategies for delirium are sparse, and the evidence is lacking for a single pharmacologic approach. Prevention with non-pharmacologic means, therefore, remains the best course of action.

Conclusion

Developing delirium after cardiac arrest is associated with increased morbidity and worse outcomes. The importance of addressing modifiable risk factors, recognizing symptoms early, and initiating coordinated treatment strategies can help to improve outcomes within this high risk population. Research investigating optimal targeted temperature management protocols, sedation depth, sedative medication choice, and other prevention strategies are required to further advance care.

Financial Support and sponsorship:

This work was supported by the Department of Anesthesiology, Critical Care Division, Vanderbilt University Medical Center, Nashville, TN, USA.

Disclosures of Funding: Dr. Boncyk receives support under the T32 research training grant from the National Institute of Health. Dr. Pandharipande is supported by a research grant from Pfizer (Hospira) Inc. in collaboration with the National Institutes of Health. Dr. Hughes is supported by an American Geriatrics Society Jahnigen Career Development Award and National Institutes of Health HL111111, R03AG045085 (Bethesda, Maryland, USA).

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Key Points:

- Patient factors leading to a cardiac arrest, initial resuscitation efforts, and post-resuscitation management all influence the potential for recovery as well as the risk for development of delirium
- Recognizing delirium in neurologically ill or post-cardiac arrest patients is difficult, but it is important in helping to identify patients at increased risk for adverse outcomes
- Once diagnosis of delirium is made, clinicians must attempt to identify and exclude all reversible causes including hypoxia, hypercarbia, hypoglycemia, metabolic derangements, sedative medication effects, infection, or continued shock

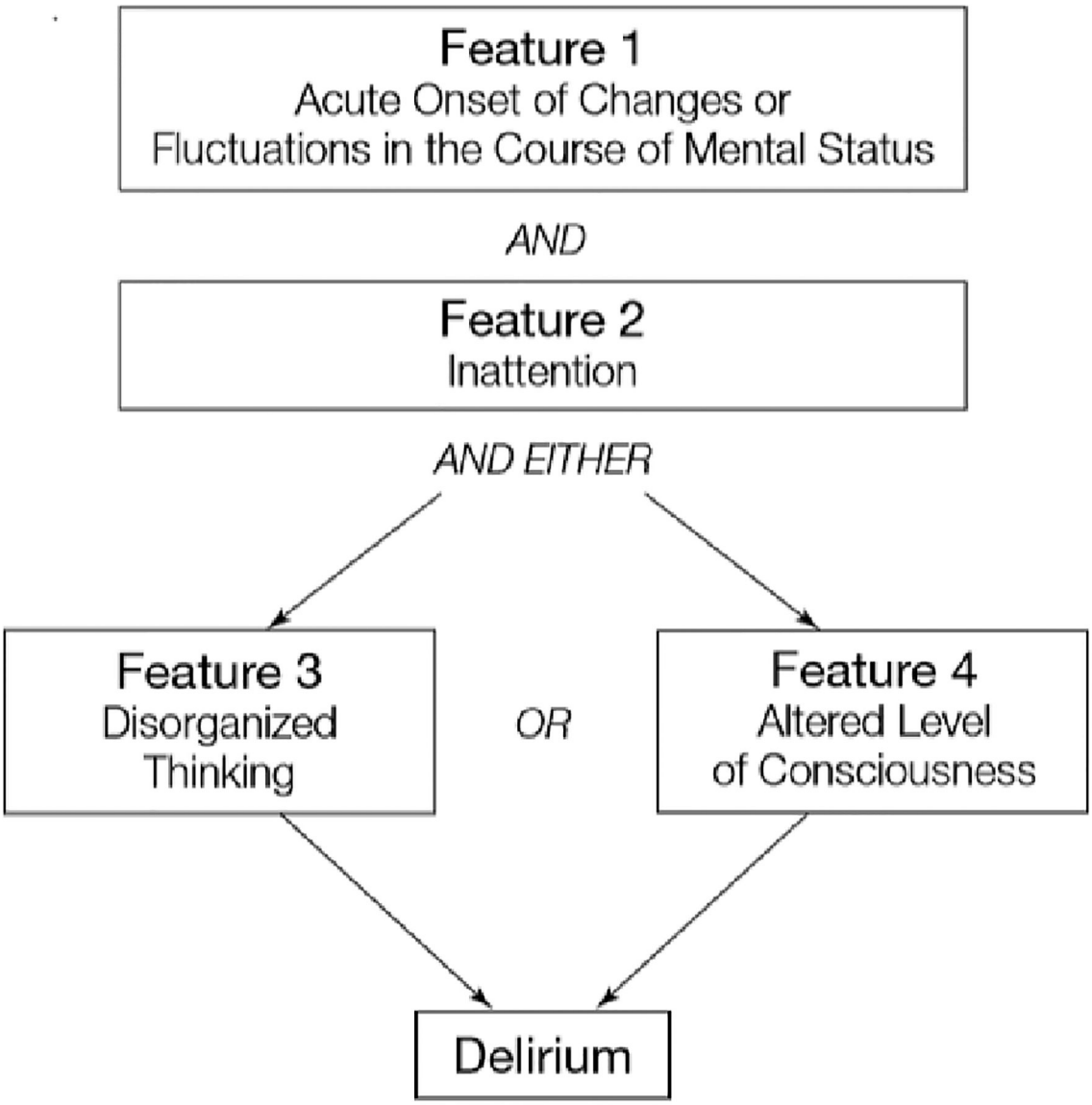

Figure 1:

Confusion Assessment Method for the Intensive Care Unit (CAM-ICU): CAM-ICU tool can be used to determine the presence or absence of delirium after the level of sedation has been assessed and determined to be greater than −3 using the Richmond Agitation-Sedation Scale (RASS).

(Previously published from Ely EW, Inouye SK, Bernard GR, et al. Delirium in mechanically ventilated patients: Validity and reliability of the confusion assessment method for the intensive care unit [CAM-ICU]. *JAMA*. 2001;286:2703–2710.) reference 37

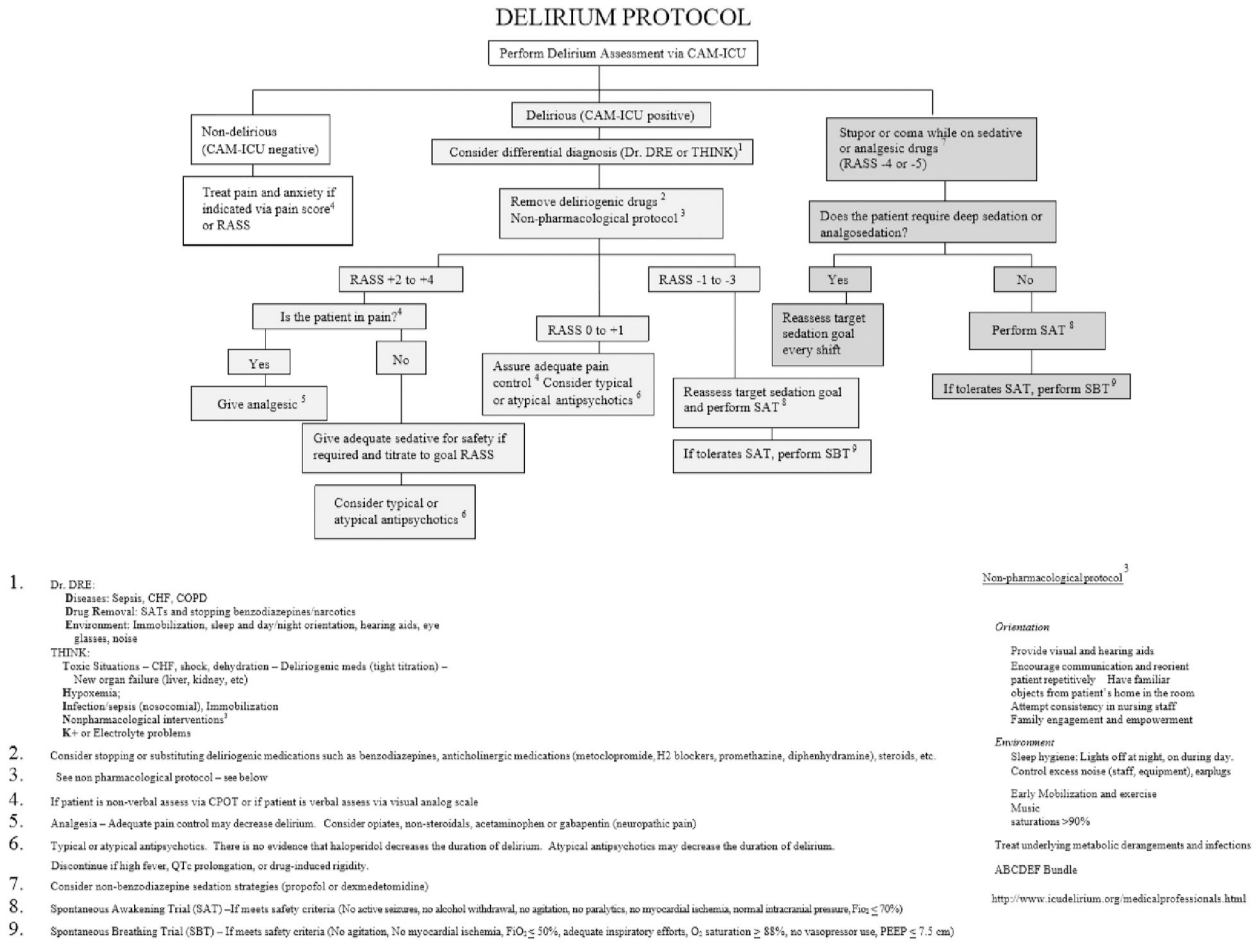

Figure 2:

Delirium Protocol for recommended use in the intensive care unit setting.

(*CAM-ICU*, Confusion Assessment Method for the Intensive Care Unit; *CHF*, congestive heart failure; *CPAP*, continuous positive airway pressure; *dx*, diagnosis; *PEEP*, positive end-expiratory pressure; *RASS*, Richmond Agitation-Sedation Scale)

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Table 1:

Modifiable and Non-Modifiable Risk Factors for Development of Delirium

Baseline	Intra-Cardiac Arrest	Post-Resuscitation
Age (> 65 years)	Compliance with ACLS Guidelines	Acidosis
Alcoholism	Duration of Resuscitation	Anticholinergic drugs
Chronic Obstructive Pulmonary Disease (COPD)	Location (in-hospital vs community)	Alcohol or drug withdrawal
Cognitive impairment or Dementia	Quality of CPR	Anemia
Depression		Fever, infection, sepsis
Gender (Male)		Hypotension
History of delirium		Metabolic disturbances (e.g., sodium, calcium, blood urea nitrogen, bilirubin, albumin)
Hypertension		Sedation (deep versus moderate/light)
Smoking		Sleep disturbances
Vision or hearing impairment		Targeting Temperature Management *

Key:

* indicates potential risk factor