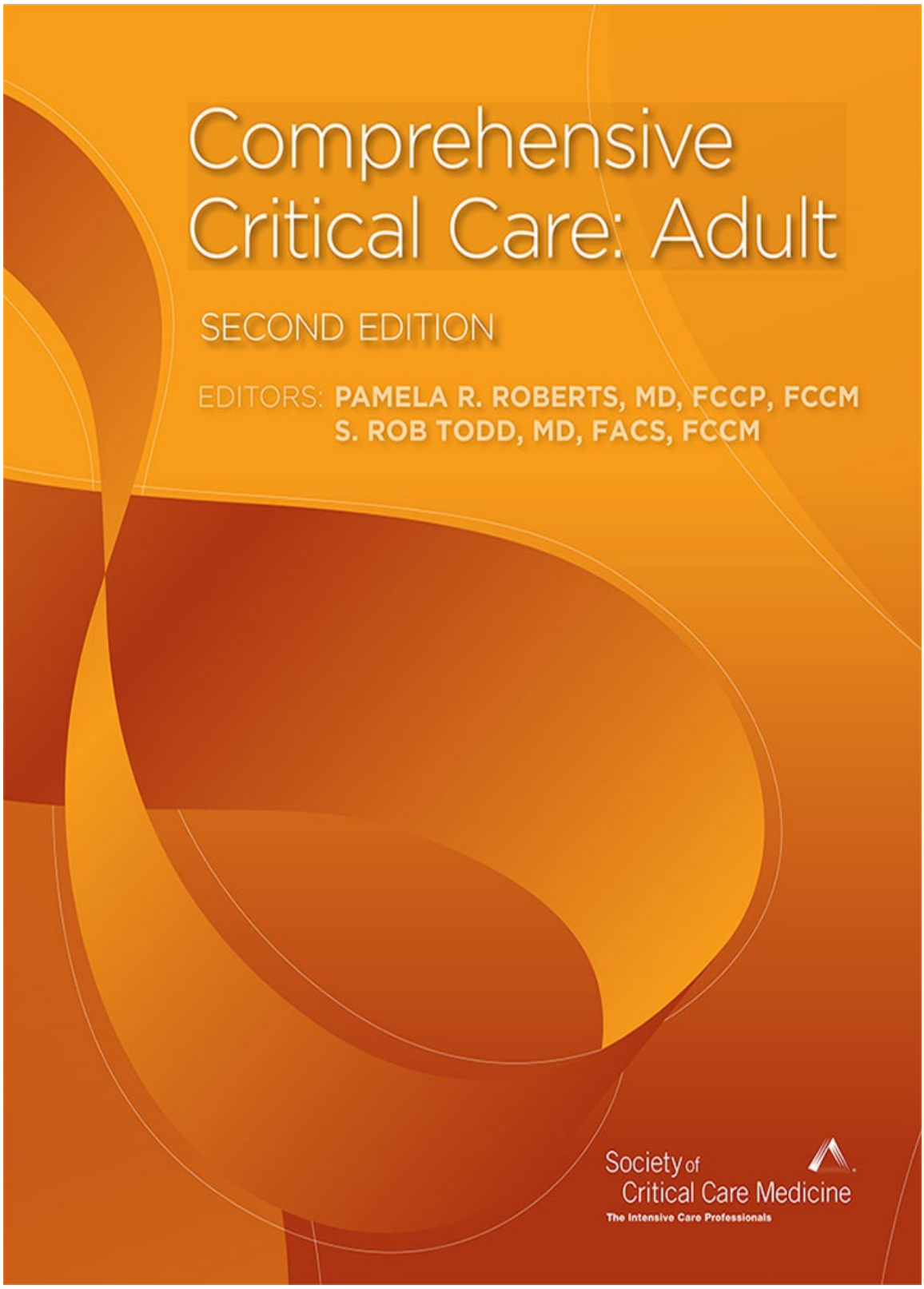
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EDITORS: PAMELA R. ROBERTS, MD, FCCP, FCCM
S. ROB TODD, MD, FACS, FCCM
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The Intensive Care Professionals

Comprehensive Critical Care: Adult

Second Edition

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Contents

CHAPTER 1

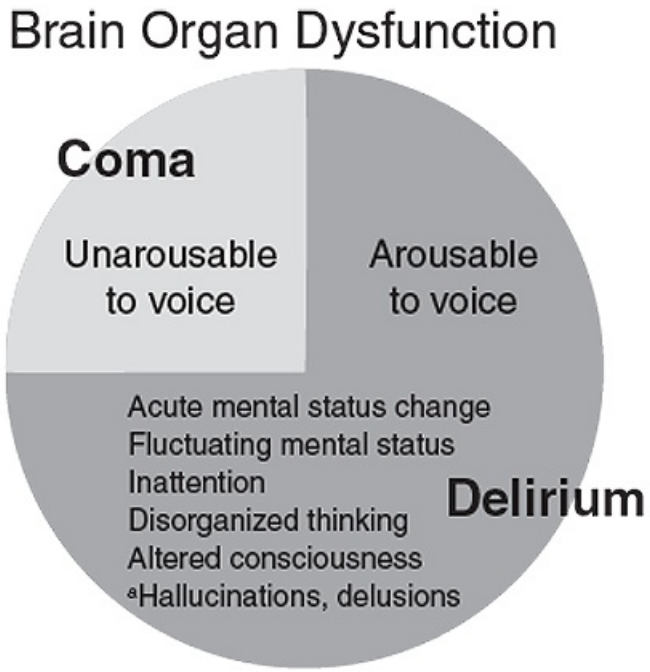
Altered Mental Status During Critical Illness: Delirium and Coma

Stuart McGrane, MBChB, MSCI, Pratik P. Pandharipande, MD, MSCI, and Christopher G. Hughes, MD

Key words: delirium, coma, Confusion Assessment Method for the Intensive Care Unit (CAM-ICU), Intensive Care Delirium Screening Checklist (ICDSC), Richmond Agitation-Sedation Scale (RASS)

Critically ill patients often manifest varying degrees of altered mental status secondary to their acute disease processes or as a consequence of the therapies used to treat disease. These mental status changes range from coma to hyperactive delirium. A comatose patient is unresponsive to physical or verbal stimuli, whereas delirium is an acute and fluctuating disorder of consciousness characterized by inattention, disorganized thinking, and perceptual disturbances (**Figure 1**). Alterations in mental status have traditionally been considered expected consequences of critical illness, and clinicians are increasingly aware that these mental status changes are manifestations of acute brain organ dysfunction that are associated with worse clinical outcomes. Early studies evaluating coma and delirium were hampered by the many different terms (eg, *confusional state, ICU psychosis, acute brain dysfunction*, and *encephalopathy*) used to describe altered mental status during critical illness. Additionally, the lack of validated bedside tools (besides the comprehensive *Diagnostic and Statistical Manual of Mental Disorders*) to diagnose delirium prevented the incorporation of delirium monitoring into routine clinical care in the ICU.

Figure 1. Delineation between delirium and coma, highlighting the cardinal symptoms of delirium



[a]Optional symptoms of delirium (may be present but are not required for the diagnosis of delirium).

DIAGNOSIS OF ACUTE BRAIN DYSFUNCTION

Traditionally, many scales have been available to assess the level of sedation and agitation in ICU patients, including the Ramsay scale, Riker Sedation-Agitation Scale (SAS), motor activity assessment scale, and Richmond Agitation-Sedation Scale (RASS). The recent guidelines on pain, agitation, and delirium from the Society of Critical Care Medicine recommend the use of the RASS and SAS due to their psychometric properties and validity in critically ill patients. The RASS (**Figure 2**) also has been shown to detect variations in the patient's level of consciousness over time or in response to changes in sedative and analgesic drug use. As a first step in assessing the level of consciousness, a sedation-agitation scale should be used. Patients who are unresponsive to verbal commands (eg, a RASS -4 or-5) are considered to be in a coma and cannot be evaluated for delirium at that time. Patients who are responsive to verbal stimuli (eg, RASS -3 and lighter) can further be evaluated for the content of that arousal via the use of delirium monitoring instruments.

Figure 2. The Richmond Agitation-Sedation Scale (RASS)

Score	Term	Description
+4	Combative	Overtly combative, violent, immediate danger to staff
+3	Very agitated	Pulls or removes tubes or catheters; aggressive
+2	Agitated	Frequent nonpurposeful movement, fights ventilator

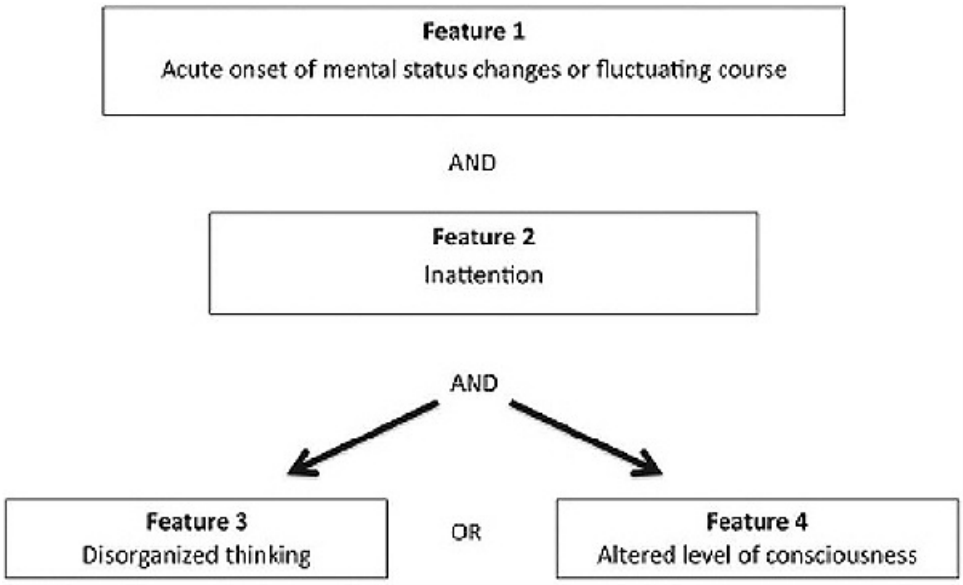
+1	Restless	Anxious but movements not aggressive or vigorous	
0	Alert and calm		
-1	Drowsy	Not fully alert but has sustained awakening (eye-opening or eye contact) to *voice* (≥10 seconds)	Verbal Stimulation
-2	Light sedation	Briefly awakens with eye contact to *voice* (<10 seconds)	
-3	Moderate sedation	Movement or eye opening to *voice* (but no eye contact)	
-4	Deep sedation	No response to voice but movement or eye opening to *physical* stimulation	Verbal Stimulation
-5	Unarousable	No response to *voice or physical* stimulation	

The scale is a 10-point scale with discrete criteria to distinguish levels of agitation and sedation.
If RASS is -4 or -5, then stop and reassess the patient at a later time for delirium, since the patient is comatose. If RASS is above -4 (-3 through +4), proceed to delirium assessment.
Reproduced with permission from Dr. E. Wesley Ely (www.icudelirium.org).

The validation of the Confusion Assessment Method for the ICU (CAM-ICU) (**Figure 3**) and the Intensive Care Delirium Screening Checklist (ICDSC) (**Table 1**) has resulted in a significant increase in delirium diagnosis, monitoring, and research. The CAM-ICU assesses 4 features of brain function: acute change or fluctuation in mental status (feature 1), inattention (feature 2), disorganized thinking (feature 3), and an altered level of consciousness (feature 4). The diagnosis of delirium using the combination of the RASS scale and the CAM-ICU requires the following:

1. RASS score of -3 or higher *and*
2. Feature 1 of CAM-ICU (acute change or fluctuation in mental status) *and*
3. Feature 2 of CAM-ICU (inattention) *and*
4. One of the following:
    a. Feature 3 (disorganized thinking) *or*
    b. Feature 4 (altered level of consciousness)

Figure 3. Confusion Assessment Method for the Intensive Care Unit (CAM-ICU)



Patients are considered to have delirium if they have Richmond Agitation-Sedation Scale scores of -3 and above (see **Figure 2**) and are considered CAM-ICU positive by having features 1 and 2 present and either feature 3 or feature 4 positive.
Adapted with permission the Society of Critical Care Medicine. ICU Liberation. www.iculiberation.org. January 2013.

Table 1. Intensive Care Delirium Screening Checklist[a]

Patient Evaluation	Characteristics	Yes	No
Altered level of consciousness	A: No response (0) B: Response to intense and repeated stimulation (loud voice and pain) (0) C: Response to mild or moderate stimulation (1) D: Normal wakefulness (0) E: Exaggerated response to normal stimulation (1)	1	0
Inattention	Difficulty in following a conversation or instructions Easily distracted by external stimuli Difficulty in shifting focuses	1	0
Disorientation	Any obvious mistake in time, place, or person	1	0

Hallucinations, delusion, psychosis	Unequivocal hallucination or behavior likely due to hallucination or delusion Gross impairment in reality testing	1	0
Psychomotor agitation or retardation	Hyperactivity requiring additional sedative drugs or restraints Hypoactivity or clinically noticeable psychomotor slowing	1	0
Inappropriate speech or mood	Inappropriate, disorganized, or incoherent speech Inappropriate display of emotion related to events or situation	1	0
Sleep-wake cycle disturbance	Sleeping <4 h or waking frequently at night (not initiated by medical staff or loud environment) Sleeping during most of the day	1	0
Symptom fluctuation	Fluctuation of the manifestation of any item or symptom over the course of 24 h	1	0

[a]Total score (0-8). A score ≥4 indicates delirium.

The ICDSC uses 8 diagnostic features to evaluate brain function. A diagnosis of delirium requires 4 or more features from the checklist to be present during the evaluation period. Additionally, patients who have some features from the ICDSC but who do not meet all the requisite criteria for delirium diagnosis are considered to have subsyndromal delirium. This part of the spectrum of acute brain dysfunction has not been fully characterized but likely lies between normal and full feature delirium and is associated with worse outcomes than normal cognition but better outcomes than delirium. A complete description of delirium monitoring tools and training materials (including clinical vignettes and translations of the CAM-ICU) can be found at www.icudelirium.org.

PREVALENCE AND PATHOGENESIS OF BRAIN DYSFUNCTION

The prevalence of acute brain dysfunction in the ICU varies according to the nature and severity of illness in the population studied. Rates of delirium in critically ill, mechanically ventilated patients are upward of 50%, and many studies in medical, surgical, trauma, and burn ICUs report rates between 50% and 80%. Rates of delirium are between 20% and 40% in cardiac ICU patients and in ICU patients with lower severity of illness who do not require mechanical ventilation. Despite increasing research in the field, the multifactorial pathophysiological process of delirium and coma remains poorly understood. Numerous hypotheses exist and include neurotransmitter imbalance (eg, dopamine, ***γ***-aminobutyric acid, and acetylcholine), inflammatory perturbations (eg, tumor necrosis factor α, interleukin 1, and other cytokines and chemokines), endothelial and blood-brain barrier dysfunction, impaired oxidative metabolism, cholinergic deficiency, and changes in various amino acid precursors. Additionally, neuroanatomical changes that include atrophy and white matter track changes have been associated with delirium.

OUTCOMES ASSOCIATED WITH BRAIN DYSFUNCTION

Acute brain organ dysfunction in critically ill patients has been demonstrated to be independently associated with worse clinical outcomes. Patients experiencing delirium have been shown to take longer time to wean from mechanical ventilation. They have increased ICU and hospital length of stay and are more likely to be readmitted to the hospital after discharge. Consequently, the presence of delirium is associated with significantly higher ICU and hospital costs. Furthermore, patients with delirium have higher mortality, and each additional day of delirium is associated with an increased risk of dying. Studies assessing the attributable mortality of delirium in the ICU have found that delirium that persists for 2 or more days increases absolute mortality, but shorter durations of delirium more likely contribute to increased mortality through prolonged ICU length of stay. The outcomes following delirium associated with sedation were recently studied in a cohort of 102 patients. The study defined rapidly reversible sedation-related delirium as delirium that was present while the patient was receiving sedation but that reversed within 2 hours of stopping sedation. This occurred in a small subset of patients (12%), whereas the majority of patients (77%) receiving sedation had persistent, nonreversible delirium. The patients with rapidly reversible delirium had outcomes similar to patients with no delirium, but the patients with persistent delirium had significantly worse outcomes, including increased mortality and institutionalization. This attests to the fact that delirium is not benign, even in patients receiving sedation, and needs to be actively monitored and managed.

Although delirium along with coma represents acute brain dysfunction, many critically ill patients also have long-term cognitive impairment that may persist for months to years after their hospitalization, significantly affecting their quality of life. Among patients who survive their critical illness, upward of 50% experience long-term cognitive impairment, about a third with deficits in the range of moderate traumatic brain injury and a quarter with deficits similar to those seen in mild Alzheimer's disease. Longer periods of delirium in the hospital are one of the strongest predictors of cognitive impairment 1 year after hospital discharge. This has led the medical profession to place increased attention and emphasis on the prevention and treatment of acute brain organ dysfunction.

RISK FACTORS FOR BRAIN DYSFUNCTION

Contributing sources can be summarized as patient-related factors (eg, age, previous dementia, diabetes, heart failure) or iatrogenic risk factors (eg, psychoactive medications, hypoxemia, shock, hypothermia, sleep deprivation) (**Table 2**). Importantly, sedative regimens, medications, and sleep hygiene are risk factors that may be modifiable by clinicians, and such modifications should be considered in order to decrease the development and/or duration of delirium in critical care patients. The temporal association between psychoactive medications and delirium in critically ill patients has been examined in different ICU cohorts. In a cohort of mechanically ventilated medical ICU patients, lorazepam administration was found to be an independent risk factor for the daily development of delirium after adjustment for important covariates such as age, severity of illness, and presence of sepsis. In surgical, trauma, and burn ICU patients, midazolam has been associated with worse delirium outcomes. The effects of analgesic medications, specifically opioids, on acute brain dysfunction are not as consistently demonstrated as the effects

of benzodiazepines. In fact, insufficient pain relief has been shown to be a risk factor for delirium in multiple studies. Prospective cohort studies of patients with hip fractures, none of whom had preoperative delirium, have shown that higher postoperative pain scores are associated with increased incidence and duration of delirium. One study demonstrated that patients who received less than 10 mg of parenteral morphine equivalents per day were more likely to develop delirium than patients who received more analgesia. Additional studies have reported on the beneficial effects of morphine and methadone in delirium. However, providing adequate analgesia needs to be balanced with the potential risk for predisposing patients to delirium due to excess opioid administration, as meperidine and morphine have been associated with increased risk for delirium. Furthermore, strategies to reduce pain through multimodal methods such as regional anesthetic techniques and nonopioid adjuncts have been shown to reduce delirium. Thus, analgesics, including opioids, may be protective of acute brain dysfunction in patients at high risk for pain but may be detrimental if used excessively to achieve sedation.

Table 2. Risk Factors for Delirium

Host Factors	Acute Illness	Iatrogenic or Environmental
Age	Sepsis	Anticholinergic medications
Baseline comorbidity	Hypoxemia	Sedative medications
Baseline cognitive impairment	Global severity of illness	Analgesic medications
Frailty	Metabolic disturbances	Sleep disturbances

PREVENTION AND MANAGEMENT OF BRAIN ORGAN DYSFUNCTION

To prevent delirium from occurring and to manage its untoward consequences, the clinician must recognize and proactively treat reversible causes of delirium. A partial list of contributing factors in the ICU is shown in **Table 2**. Mnemonics are available to help clinicians remember risk factors. *THINK* stands for Toxic situations, Hypoxemia/hypercarbia, Infection/immobility, Nonpharmacological interventions, and K^+ or other electrolytes. *Dr. DRE* stands for Disease (sepsis, congestive heart failure), Drug Removal (benzodiazepines, antihistamines, anticholinergics), and Environment (remove restraints, orient, mobilize, improve sleep, improve day-night light patterns, etc). Beyond that, just as the potential causes of delirium are multifactorial, the approach to prevention and management must be multifaceted.

Delirium and Coma Prevention

A landmark study of non-ICU medical patients reduced the development of delirium by 40% by focusing on several key goals, including regular provision of stimulating activities, a nonpharmacological sleep protocol, early mobilization activities, appropriate and early removal of catheters and restraints, optimization of sensory input, and attention to hydration. Similar studies have shown a decrease in the duration and severity of delirium without affecting overall incidence; others have shown benefit only in specific subgroups or have not shown any patient benefit. Unfortunately, the efficacy of these nonpharmacological strategies in ICU patients is unknown.

Specific to the ICU population, however, early initiation of physical therapy has been associated with improved outcomes, including decreased length of stay in both the ICU and the hospital. A randomized controlled study evaluated the combination of daily interruption of sedation with physical and occupational therapy on cognitive and functional outcomes. The investigators demonstrated that patients who underwent early mobilization had an approximate 50% decrease in the duration of delirium in the ICU and hospital and had significant improvement in functional status at hospital discharge. Sleep protocols and improvements in sleep hygiene also have been shown to reduce delirium in ICU patients; however, a double-blind, randomized controlled trial of melatonin versus placebo in patients with hip fracture did not demonstrate a difference in incidence of delirium.

The choice of sedative has implications for acute brain dysfunction beyond the effects of target-based and goal-directed sedation with daily interruption of sedatives. With regard to acute brain dysfunction specifically, the Maximizing Efficacy of Targeted Sedation and Reducing Neurological Dysfunction (MENDS) study (a randomized controlled trial of dexmedetomidine versus lorazepam) provided evidence that sedation with dexmedetomidine can decrease the duration of brain organ dysfunction, with a lower likelihood of delirium development on subsequent days. Comparing dexmedetomidine with midazolam, the Safety and Efficacy of Dexmedetomidine Compared with Midazolam (SEDCOM) study demonstrated a reduction in delirium prevalence with dexmedetomidine and a shorter time on mechanical ventilation. Another randomized controlled trial, the Dexmedetomidine Compared to Morphine (DEXCOM) study, showed that dexmedetomidine reduced the duration but not the incidence of delirium after cardiac surgery as compared with morphine-based therapy. Arousability, communication, and patient cooperation were improved with dexmedetomidine sedation versus midazolam and propofol in the Dexmedetomidine Versus Midazolam for Continuous Sedation in the Intensive Care Unit (MIDEX) and Dexmedetomidine Versus Propofol for Continuous Sedation in the Intensive Care Unit (PRODEX) studies. Most recently, a randomized controlled trial of dexmedetomidine versus propofol for ICU sedation after cardiac surgery found a decreased incidence and reduced duration of delirium with dexmedetomidine. This led to a reduction in ICU time and cost related to delirium. These studies attest to the fact that reducing benzodiazepine exposure and use of dexmedetomidine can improve ICU patient outcomes with regard to acute brain dysfunction.

Studies of prophylactic antipsychotic administration to reduce the incidence or duration of delirium have had mixed results. Perioperative haloperidol prophylaxis in elderly patients undergoing hip surgery did not reduce the incidence of delirium but did decrease its duration. Haloperidol bolus followed by an infusion in elderly patients admitted to the ICU after noncardiac surgery decreased the incidence of delirium only after intra-abdominal surgeries. A before-after study of haloperidol prophylaxis in ICU patients at high risk for delirium showed significantly reduced incidence and duration of delirium. A more recent randomized controlled trial, the Haloperidol Effectiveness in ICU Delirium (HOPE-ICU) study, however, showed no difference in days alive and free of delirium or coma between patients prophylactically treated with intravenous haloperidol or placebo.

Numerous studies have examined agents for delirium prevention after cardiac surgery. A single dose of sublingual risperidone administered when patients regained consciousness reduced the incidence of delirium compared with placebo in one study. Administration of dexamethasone upon induction of anesthesia did not reduce the incidence or duration of delirium in the first 4 days after cardiac surgery. Low cholinergic activity and anticholinergic medications have been associated with delirium, but a randomized controlled trial of rivastigmine versus placebo found no difference in the incidence of postoperative delirium.

The anti-inflammatory effects of statin medications have generated interest in delirium research. Statin therapy while in the ICU has been shown in 2 studies to be associated with lower overall risk of delirium, and increasing duration of statin discontinuation in chronic statin users increases the odds of developing delirium. Further evidence from randomized controlled trials is needed to provide evidence of the ability of statins to prevent delirium.

As a result of increasing evidence of the harm of deep sedation, multiple methods have been evaluated to decrease patients' psychoactive drug exposure. By combining daily spontaneous awakening and breathing trials, the Awakening and Breathing Controlled Trial showed a 50% reduction in sedative use, a reduction in coma and ventilator days during the ICU stay, and, most notably, a reduction in mortality at 12 months. Therefore, a liberation and animation strategy focusing on the ABCDEFs (Assessment and management of pain, Both awakening and breathing trials, Choice of sedation, Delirium monitoring and management, early Exercise, and Family involvement and empowerment) during critical illness can improve patient outcomes and likely can reduce the incidence and duration of acute and long-term brain dysfunction in critically ill patients (www.iculiberation.org). In fact, a recent study examining a similar bundle demonstrated a significant decrease in delirium and increases in mobilization, days alive, and breathing without assistance.

Delirium Management

Only after correcting contributing factors or underlying physiological abnormalities should the clinician attempt pharmacological therapy to manage delirium. Although numerous studies have examined the effects of antipsychotic medications on delirium, we still lack large randomized controlled trials in the ICU patient population comparing the efficacy of typical and atypical antipsychotics versus placebo. Small studies and case reports, therefore, provide the only data available to guide management recommendations for the antipsychotic medications most suitable for the treatment of delirium.

In one of the first studies specifically evaluating delirium in critically ill patients, olanzapine and haloperidol were shown to be equally efficacious in reducing the severity of delirium symptoms, but the lack of a placebo group makes it difficult to determine whether delirium resolved because of the drugs or because of the passage of time. In a small study of patients with delirium and orders to receive as-needed haloperidol, quetiapine was shown to be more efficacious than placebo in time to resolution of first episode of delirium. Another randomized controlled trial found that a single sublingual dose of risperidone after cardiac surgery reduced the incidence of delirium compared with placebo. The Modifying the Incidence of Delirium (MIND) study compared an atypical antipsychotic (ziprasidone) with a typical antipsychotic (haloperidol) and placebo and found no differences in brain dysfunction outcomes between groups. Rivastigmine was studied as an adjunct to haloperidol; rivastigmine was not found to decrease the duration of delirium and might have contributed to increased mortality.

Two recent studies have examined the role of dexmedetomidine in treating hyperactive delirium. In the Dexmedetomidine to Lessen Intensive Care Unit Agitation (DAHLIA) trial, patients whose weaning from mechanical ventilation was hampered by hyperactive or agitated delirium were randomized to receive up to 7 days of intravenous dexmedetomidine or placebo. Patients treated with dexmedetomidine had increased ventilator-free hours at 7 days and faster resolution of their delirium symptoms. The second study examined nonintubated ICU patients with hyperactive delirium requiring haloperidol for symptom control. Those with improved agitation after haloperidol received a haloperidol infusion, and those whose agitation did not improve received dexmedetomidine in addition to haloperidol. Patients receiving dexmedetomidine were less likely to fail the regimen, had more time with satisfactory sedation, experienced less oversedation, had a shorter ICU stay, and incurred significantly lower total costs.

Prior to starting medications in an attempt to control a patient's delirium, clinicians should consider discontinuation or dose adjustment of drugs that may be adversely affecting brain function. Although the intended use of these agents is to treat delirium and improve cognition, they all have psychoactive effects that may further cloud the sensorium and promote a longer overall duration of cognitive impairment. Therefore, use of the smallest effective dose given for the shortest necessary time may be the most important delirium management recommendation.

IMPLEMENTING A DELIRIUM MONITORING PROGRAM

When introducing a delirium monitoring program, clinicians must recognize that they are attempting to affect positive change on the prevailing culture. Successful change will start small and grow from there. Many steps are required to ensure success, and lack of attention to detail in any one area may hinder progress. The delirium monitoring program must use a tool that has been validated for the population to be monitored and must incorporate a multidisciplinary approach that includes modern training and learning methods for different learning styles prior to implementation. Some resistance will be encountered, but strategies are available to overcome these (eg, regular feedback sessions, refresher training). Incorporation of delirium data into the medical record and transparent use of this information to effect positive patient outcomes will both encourage and validate those providers who are collecting the information. The presentation of this information on bedside rounds has been referred to as the *brain map*. In this framework, the patient's current brain function and trajectory are reported each day. This should prompt discussion on the patient's overall clinical course and whether the current brain organ function is consistent with the trajectory and other organ functions. These brain map discussions should focus on risk factors (eg, benzodiazepines, sepsis) and possible management strategies (eg, physical therapy, antibiotics).

SUMMARY

Altered mental status (delirium and coma) is a prevalent and costly problem in the critical care patient population that is associated with significant

morbidity. Physicians must strive to balance the need for sedation with the cost that acute and long-term cognitive dysfunction places on both patients and society. With the appropriate attention, diagnostic tools, and medical practice, clinicians have the ability to significantly decrease the burden of this acute brain organ dysfunction. Management techniques with an integrated approach that includes alteration of sedative medication regimens, deployment of preventive strategies, initiation of delirium monitoring, judicious use of pharmacological therapy, early mobility, and improved sleep hygiene can reduce the incidence and impact of this disease in critically ill patients.

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CHAPTER 2

Seizures, Stroke, and Other Neurological Emergencies

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Key words: epilepsy, seizures, stroke, brain injury

STATUS EPILEPTICUS

Status epilepticus (SE) is a common neurological emergency, and it carries significant morbidity and mortality. Traditionally, SE has been defined as continuous or intermittent seizures lasting for more than 30 minutes with incomplete recovery of consciousness. However, the urgency in treating this condition necessitated a more conservative definition.[1] Because there is evidence that tonic-clonic seizures rarely last more than a few minutes, the traditional definition has been discounted. Similarly, animal data suggest that fixed neuronal damage and resistance to pharmacological treatment may occur after 30 minutes of continuous seizing activity. Most experts agree that a patient is in SE if seizures persist for more than 5 minutes or if the patient's state of consciousness does not recover between seizures.

Initial Evaluation and Management

During the initial evaluation, the clinician obtains the patient's relevant information, paying attention to details such as history of brain injury, onset of epilepsy diagnosis, use of antiepileptic drugs (AEDs), use of psychotropic drugs, and history of substance abuse, particularly alcohol. Simultaneous evaluation and management of the airway, breathing, and circulatory state are mandatory within the first 10 minutes of initial assessment. The main principle of critical care management of SE is to treat the seizures quickly and aggressively. About 80% of patients will respond to first-line AEDs if treatment is delivered within 30 minutes of onset, but less than 40% will respond if treated within 2 hours of onset.

The preferred first-line AED is lorazepam, based on its rapid onset and prolonged action (**Table 1**). Lorazepam is superior to diazepam in controlling seizures at the prehospital and in-hospital levels. In a study by the Veterans Affairs Status Epilepticus Cooperative Study Group,[2] treatment with lorazepam resulted in a 65% success rate versus treatment with phenobarbital (58%), diazepam plus phenytoin (56%), and phenytoin (44%); the proportion of complications, including respiratory depression, was not different among the 4 groups at 30 days. In a landmark randomized controlled clinical trial,[3] respiratory depression was less associated with benzodiazepine use in the management of SE. In the Rapid Anticonvulsant Medication Prior to Arrival Trial (RAMPART) study, intramuscular midazolam was found to be at least as effective as IV lorazepam in prehospitalized patients with SE.

The preferred second-line agent is phenytoin or fosphenytoin (**Table 1**). Although no strong reason exists for this preference, this AED is the most frequently recommended second-line agent. The efficacy of phenytoin as a second-line agent has been compared with valproic acid. Several newer AEDs such as levetiracetam and lacosamide have been proposed as co-adjuvants in the management of refractory SE (RSE), but more experience is needed before a final recommendation can be made.

Third-line agents should be considered once first and second agents fail (**Table 1**). Intravenous midazolam is the most studied agent for the management of RSE. In a systematic review, Claassen et al[4] reported that the efficacy of midazolam for the treatment of RSE was similar to that of propofol but inferior to that of pentobarbital; however, the use of midazolam was associated with more withdrawal and breakthrough seizures and fewer hemodynamic alterations. The mortality, although high, was similar in all treatment groups. Pentobarbital should be reserved for those patients failing third-line AEDs. It offers great seizure control at the expense of more complications such as hypotension, cardiac depression requiring vasopressors or inotropes, immunosuppression, and longer ICU and hospital length of stay (LOS) based on its longer half-life.

Table 1. Conventional Management Strategy for Status Epilepticus and Refractory Status Epilepticus

Stage	Time	Action	Comments
Resuscitation	0-5 min	Diagnosis ABCs • Airway • Oxygen • Obtain IV access Workup: order EEG	Obtain ABG, chemistry panel, blood cell counts, AED levels, toxicology tests Order ECG Administer thiamine, 100 mg IV Administer Dextrose 50, 25-50 g IV, unless known glucose Consider CT scan in comatose patients particularly if there are lateralizing signs and/or lumbar puncture, but don't delay administration of AEDs or antibiotics.
First-line AED	6-10 min	Lorazepam	Dose: 0.05-0.1 mg/kg over 1-2 min, repeat in 5 min Onset: 3-10 min Effect: 12-24 h Half-life: 14 h Side effects: sedation, respiratory depression (but no different than IV phenytoin), hypotension, hyperosmolar metabolic acidosis with repetitive use secondary to accumulation of propylene glycol. Each milliliter of lorazepam injection (2 mg of lorazepam per milliliter) contains 0.8 mL of propylene glycol.

		Midazolam (IM)	Dose: 0.2 mg/kg IM up to maximum of 10 mg Onset: 2-3 min Effect: 2-4 h Half-life: 2 h Side effects: respiratory depression, hypotension
Second-line AED	11-20 min	PHT or F-PHT	Dose: 20 mg/kg. Rate 150 mg/min (F-PHT), or 25-50 mg/min for PHT to avoid hypotension Onset: 20-25 min Effect: 6-8 h Half-life: 6 h Side effects: 5 to 10% of patients receiving F-PHT have hypotension, arrhythmias, respiratory depression, encephalopathy, nystagmus, ataxia, hepatotoxicity, pancytopenia, Stevens-Johnson's syndrome, hypocalcemia (F-PHT)
		Valproic acid (Some experts consider this AED a third-line agent, but data suggest that it may be more effective than phenytoin.)	Dose: 30-50 mg/kg. Rate 10 mg/min Onset: 20-25 min Effect: 6-8 h Half-life: 6 h Side effects: respiratory depression, hepatotoxicity, thrombocytopenia
		Alternatives Levetiracetam	Dose: 1,000-4,000 mg IV. Rate 30-60 mg/min
		Phenobarbital	Dose: 20 mg/kg. Rate 50-100 mg/min
		Lacosamide	Dose: 200-400 mg/kg. Rate 40-80 mg/min
Third-line AED	>20 min	*Continuous IV AED* Midazolam	Dose: 0.2-0.4 mg/kg initial bolus, repeat every 5 min until seizure stops to a total loading dose of 2 mg/kg. IV infusion 0.1 mg/kg to 2 mg/kg/h (maximum 200 mg/h). Side effects: Respiratory depression, hypotension
		Propofol	Dose: 1 mg/kg initial load, repeat 1-2 mg/kg every 3-5 min until seizures stop to a total loading dose of 10 mg/kg. IV infusion 1-15 mg/kg/h. (Do not exceed 5 mg/kg/h for >24 h because this poses a higher risk of propofol infusion syndrome.) Side effects: respiratory depression, hypotension, propofol infusion syndrome (metabolic [lactic] acidosis, rhabdomyolysis, multiple-organ failure)
		Request cEEG	
Fourth-line AED	>60 min	Pentobarbital	Dose: 5 mg/kg initial load, rate 50 mg/min, may repeat 5 mg/kg every 5 min until seizures stop to a total loading dose of 10 mg/kg. IV infusion 1-10 mg/kg/h classically titrated to "burst" suppression. Side effects: respiratory depression, hypotension, immunosuppression, examination compatible with "brain death"

Abbreviations: ABC, airway, breathing, circulation; ABG, arterial blood gas; AED, antiepileptic drug; cEEG, continuous electroencephalography; CT, computed tomography; ECG, electrocardiograph; EEG, electroencephalograph; F-PHT, fosphenytoin; IM, intramuscular; PHT, phenytoin.

ICU Management

Those patients who meet criteria for RSE and require IV AEDs should be admitted to an ICU where continuous electroencephalography (EEG), hemodynamic monitoring, and neurological assessments can be performed hourly. Most neurologists will direct IV AED therapy to a pattern of burst suppression, although directing the therapy to simpler seizure suppression may be an alternative for those intensivists with less experience in EEG monitoring. The two strategies, seizure suppression versus EEG burst suppression, were compared in a small study that showed no meaningful difference in outcomes. The study suggested that the lack of demonstrable advantage of treatment to burst suppression argues against the routine use of such an aggressive treatment. Additional options for the advanced management of RSE are listed in **Table 2**.

Table 2. Alternatives for the Management of Refractory Status Epilepticus

Antiepileptic drugs	IV levetiracetam Ketamine drip IV lacosamide Lorazepam drip Thiopental Oral topiramate
Anesthetics	Inhaled isoflurane Lidocaine
Miscellaneous medications	Verapamil Acetazolamide Paraldehyde Steroids Corticotropin IV immunoglobulin
Others	Ketogenic diet

Vagus nerve stimulation
Electroconvulsive therapy
Deep brain stimulation
Transcranial magnetic stimulation
Mild induced hypothermia (33°C-35°C; 91.4°F-95°F)

Information taken from references 12-17.

ISCHEMIC STROKE

Acute ischemic stroke (AIS) is a leading cause of morbidity and mortality in the United States. In 2015, the American Heart Association (AHA) estimated that there were 610,000 new stroke cases, 185,000 recurrent strokes, and 5,700,000 stroke survivors in the United States, many requiring long-term healthcare; in the same year, at least 150,147 deaths were attributed to stroke.

Initial Evaluation and Critical Care Management

The initial evaluation and subsequent ICU management of patients with AIS are based on 5 components: (1) diagnosis; (2) thrombolysis, recanalization, and reperfusion; (3) prevention of infarct expansion, recurrence, and hemorrhagic conversion; (4) prevention and treatment of malignant cerebral edema; and (5) prevention and management of medical and neurological complications.

Diagnosis

The diagnosis of AIS is made by clinical factors, computed tomography (CT), and magnetic resonance imaging (MRI). Initial neurological evaluation and calculation of the National Institutes of Health Stroke Scale (NIHSS) (**Table 3**) allow for estimation of stroke burden and potential neurological outcome and for objective patient follow-up in the ICU. A noncontrast CT of the brain helps to rule out intracranial mass lesions and hemorrhages. MRI is used in some centers as part of early diagnostic and management algorithms in AIS. The use of telemedicine has the potential to improve the accuracy in diagnosis of AIS.

Table 3. The National Institutes of Health Stroke Scale (NIHSS)

NIH Stroke Scale Item	Scoring Definitions	Score
1a. LOC	0 – alert and responsive 1 – arousable to minor stimulation 2 – arousable only to painful stimulation 3 – reflex responses or unarousable	
1b. LOC Questions—Ask pt's age and month. Must be exact.	0 – Both correct 1 – One correct (or dysarthria, intubated, foreign lang) 2 – Neither correct	
1c. Commands—open/close eyes, grip and release non-paretic hand, (Other 1-step commands or mimic ok)	0 – Both correct (ok if impaired by weakness) 1 – One correct 2 – Neither correct	
2. Best Gaze—Horizontal EOM by voluntary or Doll's.	0 – Normal 1 – partial gaze palsy; abnl gaze in 1 or both eyes 2 – Forced eye deviation or total paresis which cannot be overcome by Doll's.	
3. Visual Field—Use visual threat if nec. If monocular, score field of good eye.	0 – No visual loss 1 – Partial hemianopia, quadrantanopia, extinction 2 – Complete hemianopia 3 – Bilateral hemianopia or blindness	
4. Facial Palsy—If stuporous, check symmetry of grimace to pain.	0 – Normal 1 – minor paralysis, flat NLF, asymm smile 2 – partial paralysis (lower face – UMN) 3 – complete paralysis (upper & lower face)	
5. Motor Arm—arms outstretched 90 deg (sitting) or 45 deg (supine) for 10 secs. Encourage best effort. Circle paretic arm in score box	0 – No drift × 10 secs 1 – Drift but doesn't hit bed 2 – Some antigravity effort, but can't sustain 3 – No antigravity effort, but even minimal mvt counts 4 – No movement at all	L or R

	X – unable to assess due to amputation, fusion, fx, etc.	
6. Motor Leg—raise leg to 30 deg supine × 5 secs.	0 – No drift × 5 secs 1 – Drift but doesn't hit bed 2 – Some antigravity effort, but can't sustain 3 – No antigravity effort, but even minimal mvt counts 4 – No movement at all X – unable to assess due to amputation, fusion, fx, etc.	L or R
7. Limb Ataxia—check finger-nose-finger; heel-shin; and score only if out of proportion to paralysis	0 – No ataxia (or aphasic, hemiplegic) 1 – ataxia in upper or lower extremity 2 – ataxia in upper AND lower extremity X – unable to assess due to amputation, fusion, fx, etc.	L or R
8. Sensory—Use safety pin. Check grimace or withdrawal if stuporous. Score only stroke-related losses.	0 – Normal 1 – mild-mod unilateral loss but pt aware of touch (or aphasic, confused) 2 – Total loss, pt unaware of touch. Coma, bilateral loss	
9. Best Language—Describe cookie jar picture, name objects, read sentences. May use repeating, writing, stereognosis	0 – Normal 1 – mild-mod aphasia; (diff but partly comprehensible) 2 – severe aphasia; (almost no info exchanged) 3 – mute, global aphasia, coma. No 1 step commands	
10. Dysarthria—read list of words	0 – Normal 1 – mild-mod; slurred but intelligible 2 – severe; unintelligible or mute X – intubation or mech barrier	
11. Extinction/Neglect—simultaneously touch patient on both hands, show fingers in both vis fields, ask about deficit, left hand.	0 – Normal, none detected. (vis loss alone) 1 – Neglects or extinguishes to double simult stimulation in any modality (vis, aud, sens, spatial, body parts) 2 – profound neglect in more than one modality	

Information taken from National Institute of Neurological Disorders and Stroke (NINDS). National Institute of Neurological Disorders and Stroke (NINDS). http://www.ninds.nih.gov. Accessed June 15, 2016.

Thrombolysis and Recanalization

After 1995, the treatment of AIS was revolutionized by the results of the National Institutes of Neurological Disorders and Stroke (NINDS) trial.[5] Intravenous recombinant tissue plasminogen activator (r-tPA) was initially approved in the United States for use in eligible patients within 3 hours of AIS onset. The recent results of the European Cooperative Acute Stroke Study (ECASS-III) trial confirmed the safety and efficacy of IV r-tPA in AIS patients within 4.5 hours of onset.[6] Recent clinical trials have demonstrated that endovascular reperfusion of acutely occluded large cerebral arteries through mechanical thrombolysis improves mortality and functional outcome in eligible AIS patients. The maximal time window for successful clinical recovery after reperfusion is within 6 to 8 hours for middle cerebral artery (MCA) or internal carotoid artery (ICA) occlusions and possibly 12 to 24 hours for basilar artery occlusions.

Prevention of Infarct Expansion, Recurrence, or Hemorrhagic Conversion

This phase is achieved by tight blood pressure control, temperature regulation, glycemic control, and secondary stroke prevention. Studies have reported a U-shaped relationship where poor outcome was associated with especially low and especially high admission blood pressure levels. Current guidelines from the AHA and the American Stroke Association recommend withholding antihypertensive therapy for AIS unless there is planned thrombolysis (treat to keep systolic blood pressure [SBP] <180 mm Hg or diastolic blood pressure <105 mm Hg), there is evidence of concomitant noncerebral hypertensive organ damage (eg, acute myocardial ischemia, aortic dissection, pulmonary edema, or renal failure), or the blood pressure is excessively high (SBP >220 or diastolic blood pressure >120 mm Hg), cutoffs that have been arbitrarily determined based on the upper limit of normal cerebral autoregulation.

Hemorrhagic transformation is seen in up to 9% of AIS patients. This devastating complication should be suspected in deteriorating patients with large territorial infarction, cardioembolism, systemic anticoagulation, recent thrombolytic therapy, or uncontrolled hypertension. After administration of IV r-tPA, risk factors for hemorrhagic conversion include a large area of infarction, older age, hyperglycemia, uncontrolled hypertension, congestive heart failure, and prior treatment with aspirin.

Prevention and Treatment of Malignant Cerebral Edema

MCA infarction is associated with higher morbidity and mortality compared to other infarcts. MCA strokes with an NIHSS score of less than 20, thrombus at the carotid terminus location, presence of nausea and vomiting, elevated white blood cell count, early involvement of more than 50% of the MCA territory on CT scans, and additional involvement of the anterior cerebral artery territory and/or posterior cerebral artery territory may be associated with worse edema and intracranial hypertension (**Figure 1**). Management of cerebral edema and elevated intracranial pressure (ICP) follows the same principles described in **Table 4** for other neurological emergencies. Analgesia, sedation, mechanical ventilation, and hyperventilation should be used to transiently achieve a $Paco_2$ of 30 to 35 mm Hg, and hyperosmolar therapy with 20% mannitol or 23.4% saline should be administered. Surgery may offer additional survival benefit to refractory cases of elevated ICP and mass effect.

Figure 1. Left large hemispheric infarct with subfalcine herniation

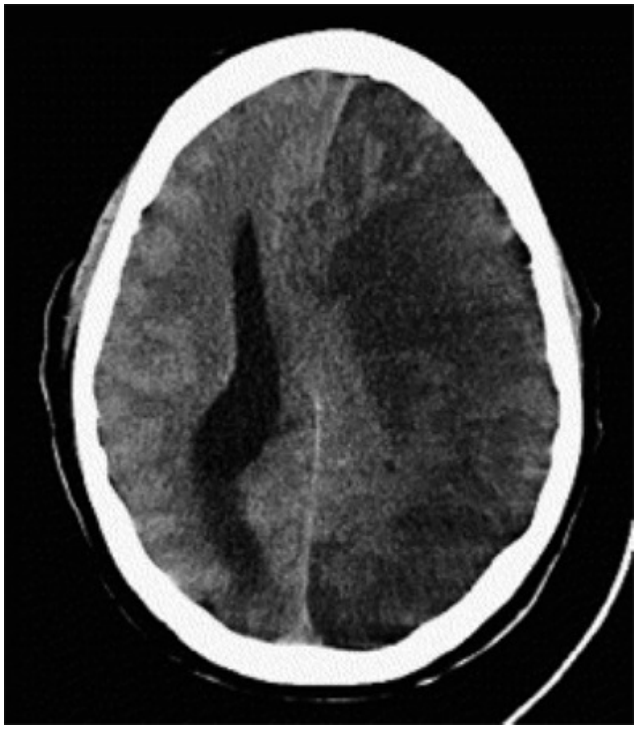

Table 4. Stepwise Approach for Management of Intracranial Pressure

CSF drainage	Initial CSF drainage may be a lifesaving procedure, particularly in the setting of hydrocephalus and IVH. This technique allows for rapid clearance of CSF, release of ICP, and ICP/CPP monitoring. As a general rule, an ICP monitor or EVD should be placed in all comatose patients (Glasgow Coma Scale score ≤8) with the goal of maintaining ICP <20 mm Hg and CPP >70 mm Hg, unless their condition is so dismal that aggressive ICU care is not warranted. Compared with parenchymal monitors, EVDs carry the therapeutic advantage of allowing CSF drainage and the disadvantage of a substantial risk of infection (approximately 10% during the first 10 days).
Sedation	Sedation should be used to minimize pain and agitation and decrease surges in the ICP. Agitation must be avoided, because it can aggravate ICP elevation through straining (increasing thoracic, jugular venous, and systemic blood pressure), increase $CMRO_2$, and cause uncontrolled hyperventilation or hypoventilation, both of which can be detrimental. During an ICP spike, sedation may be all that is necessary to control the ICP. The goal of sedation should be a calm, comfortable, and cooperative state in patients with ICP that is well controlled, and a quiet, motionless state in patients in whom ICP elevation requires active management. The preferred regimen is the combination of a short-acting opioid such as fentanyl (1-3 µg/kg/h) or remifentanil (0.03-0.25 µg/kg/min) to provide analgesia, and propofol (0.3-3 mg/kg/h) because of its extremely short half-life, which makes it ideal for periodic interruption for neurological assessments; this regimen should be performed daily unless the patient's ICP is too unstable (frequent ICP crisis in the setting of awakening, position changes, fever) to tolerate this. Bolus injections of opioids should be used with caution in patients with elevated ICP because these agents can transiently lower MAP and increase ICP due to autoregulatory vasodilation of cerebral vessels. In one trial, propofol (compared with an opioid-based sedation regimen) was associated with lower ICP and fewer ICP interventions in patients with severe traumatic brain injury. However, propofol has been associated with mitochondrial dysfunction and multiple-organ failure (propofol infusion syndrome). Predisposing factors include young age, severe critical illness of central nervous system or respiratory origin, exogenous catecholamine or glucocorticoid administration, inadequate carbohydrate intake, and subclinical mitochondrial disease.
CPP optimization	Two prevailing strategies for the management of elevated ICP have evolved from the experience in traumatic brain injury. The Lund concept assumes a disruption of the BBB and recommends manipulations to decrease the hydrostatic BP and increase osmotic pressures in order to minimize cerebral blood volume and vasogenic edema by improving perfusion and oxygenation to the injured areas of the brain. This is achieved in theory by maintaining a euvolemic state with normal hemoglobin, hematocrit, and plasma protein concentrations and by antagonizing vasoconstriction through reduction of catecholamine concentration in plasma and sympathetic outflow. These therapeutic measures attempt to normalize all essential hemodynamic parameters (blood pressure, plasma oncotic pressure, plasma and erythrocyte volumes, Pao_2, and $Paco_2$).The introduction of microdialysis with novel physiological targets may optimize the goals of the original Lund protocol. The Rosner concept emphasizes maintaining a high CPP to minimize reflex vasodilatation or ischemia at the expense of added cardiopulmonary stress. Computerized bedside graphic displays (eg, the ICU Pilot, CMA Microdialysis, Solna, Sweden) can allow clinicians to identify whether ICP and MAP are positively correlated, in which case a low CPP would be preferable, or negatively correlated, in which case a higher CPP would be desirable.
Hyperosmolar therapy	Hyperosmolar therapy should be used after sedation and CPP optimization fail to normalize ICP. The initial dose of mannitol is 1-1.5 g/kg of a 20% solution, followed by bolus doses of 0.25-1.0 g/kg as needed to a target osmolality of 300-320 mOsm/kg. Additional