

REVIEW ARTICLE

Challenges of Delirium Management in Patients with Traumatic Brain Injury: From Pathophysiology to Clinical Practice

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Abstract: Traumatic brain injury (TBI) can initiate a very complex disease of the central nervous system (CNS), starting with the primary pathology of the inciting trauma and subsequent inflammatory and CNS tissue response. Delirium has long been regarded as an almost inevitable consequence of moderate to severe TBI, but more recently has been recognized as an organ dysfunction syndrome with potentially mitigating interventions. The diagnosis of delirium is independently associated with prolonged hospitalization, increased mortality and worse cognitive outcome across critically ill populations. Investigation of the unique problems and management challenges of TBI patients is needed to reduce the burden of delirium in this population.

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In this narrative review, possible etiologic mechanisms behind post-traumatic delirium are discussed, including primary injury to structures mediating arousal and attention and secondary injury due to progressive inflammatory destruction of the brain parenchyma. Other potential etiologic contributors include dysregulation of neurotransmission due to intravenous sedatives, seizures, organ failure, sleep cycle disruption or other delirium risk factors. Delirium screening can be accomplished in TBI patients and the presence of delirium portends worse outcomes.

There is evidence that multi-component care bundles including an analgesia-prioritized sedation algorithm, regular spontaneous awakening and breathing trials, protocolized delirium assessment, early mobility and family engagement can reduce the burden of ICU delirium. The aim of this review is to summarize the approach to delirium in TBI patients with an emphasis on pathogenesis and management. Emerging CNS-active drug therapies that show promise in preclinical studies are highlighted.

Keywords: Traumatic brain injury, critical care, delirium, electroencephalography, post-traumatic delirium, dexmedetomidine, barbiturates, xanthohumol.

1. INTRODUCTION

Approximately half of the patients admitted to surgical intensive care units (ICUs) for traumatic brain injury (TBI) suffer from delirium at some point during their admission, and this number increases to 75% for patients over 50 years

of age [1, 2]. Delirium is an acute alteration in mental status characterized by confusion, inattention and fluctuating levels of arousal. Post-traumatic agitation and delirium typically present within the first 24 hours of a TBI admission but may develop at any point during the hospital stay and is also prevalent during the rehabilitation period. Up to 70% of patients transferred to inpatient neurorehabilitation for TBI suffer from delirium upon arrival. This devastating form of brain dysfunction is linked to increased 6-month mortality, longer hospital stays and increased costs of care among ICU

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patients [3-6]. Duration of delirium is an independent predictor of worse long-term cognitive impairment in this population [7].

Delirium is described in the American Psychiatric Association's Diagnostic and Statistical Manual – 5th Edition (DSM-5) as an acute confusional state defined by disturbances in attention, awareness, or cognition developing over hours to days due to disease or sedation that is not better explained by an alternative diagnosis or a comatose state [8]. The gold standard for diagnosis of delirium is with bedside examination by a trained psychiatry professional and can be formally assessed in the inpatient setting using the Delirium Rating Scale (DRS-R98) [9]. The most widely used tool for delirium assessment across medical and surgical ICUs is the Confusion Assessment Method for the ICU (CAM-ICU) [10], by which caretakers assess patients in four cardinal domains: fluctuating mental status; inattention; disorganized thinking; and altered level of consciousness. The Intensive Care Delirium Screening Checklist (ICDSC) is also widely used and comprises eight items: level of consciousness, inattention, psychosis (*e.g.* hallucinations or delusions), psychomotor agitation or retardation, inappropriate speech or mood, sleep wake/cycle disturbance and symptom fluctuation [11]. Typically among TBI patients, the most common screen for neurologic dysfunction in the pre-hospital, emergency and surgical context is the Glasgow Coma Scale (GCS), which scores patients on a 15-point scale by the level of arousal and quality of motor and verbal responses to stimuli [12]. Scores 13 and above on presentation reflect mild TBI and 9-12 reflect moderate TBI. GCS scores below 9 within 48 hours of presentation are considered as severe TBI [13].

Patients with delirium may have a GCS score ranging from 9 to 14, and patients with GCS less than 9 are typically considered to be in coma. Lower GCS scores on admission have long been associated with increased mortality, worse neurocognitive outcomes. Patients with post-traumatic delirium are also at risk for severe acute and long-term psychiatric consequences [14-16]. Delirium often remains unnoticed if not actively screened for in the ICU [17]; therefore, prevention, early identification, and effective management of delirium are critical aspects of ICU care. Despite delirium being clearly defined clinically and very common among TBI patients, its pathogenesis requires further studies to elucidate specifically designed therapeutic targets. Recently elucidated pathogenetic mechanisms of neurotrauma in the model of spinal cord injury may prove helpful in re-evaluation of existing therapies used for delirium in the clinical setting and also in specifically designed pre-clinical studies.

The remainder of this manuscript is geared toward understanding the myriad etiologies that predispose toward delirium in trauma patients, manifestations, typical findings on clinical studies and principles of management. We provide an overview of the current state of knowledge regarding mechanistically-driven pharmacologic therapies and conclude with comments on the gaps in current literature with an eye to future potential investigations.

2. ETIOLOGIES AND PATHOBIOLOGY OF DELIRIUM IN BRAIN INJURY PATIENTS

Effective management of delirium in TBI patients requires first an understanding of the various potential etiologies of delirium in this population. Etiologies of particular relevance to TBI patients include focal or diffuse brain dysfunction due to the primary injury, as well as secondary injury due to increased intracranial pressure (ICP) from hemorrhage or edematous states sustained by severe, prolonged inflammation and vasogenic edema [18, 19]. Yet post-traumatic delirium can occur even in mild or moderate TBI patients, for whom no major structural injury is evident on neuroimaging. The underlying pathophysiology is incompletely understood, but a severe destructive and very protracted inflammation is associated with a cascade of molecular, biochemical, and cellular changes within the brain that lead to neuronal damage and apoptosis [20]. Additional etiologies that are common across critically ill populations include adverse effect of intravenous sedatives or other drugs, organ failure leading to metabolic compromise, sepsis resulting in systemic inflammatory response, and conditions of the ICU environment that can result in sleep deprivation, overstimulation, sensory deprivation and psychological stress. In many cases these risk factors occur in the presence of pre-existing neurodegenerative or psychiatric pathology, which further increases delirium risk. Fig. 1 provides an overview of the etiologic risk factors of delirium in TBI patients. In the following subsections, we provide a conceptual framework for pathophysiological contributions of these risk factors, and in subsequent sections, we discuss associated clinical studies and principles of delirium management in this population.

2.1. Primary Injury

The most common type of injury sustained in closed-skull TBI is a coup-contrecoup pattern. This stems from excessive acceleration due to an external impact followed by deceleration with the impact of brain parenchyma against the enclosing skull and resultant contusions of the cortex and underlying white matter [21]. Fast torqueing acceleration and deceleration can also result in TBI. Both patterns of injury result in the shearing of long axonal fiber tracts and damage to the cortical layers [22]. A locally massive injury to the white matter can initiate a severe prolonged inflammation fuelled by an abundance of potentially immunogenic myelin debris and hemorrhages [18]. In this context, the initial injury likely plays a large role in the development of delirium through direct impairment of neuroanatomical areas modulating normal resting-state functional networks, and disruptions in interregional connectivity on which these networks rely [20].

In case of penetrating injuries, breach of the skull table and dural layers as well as hemorrhage due to vessel injury and inflammatory responses to foreign body and its accompanying antigens can also play a role [23]. In addition to the mechanisms described above, there may be diffuse edema, first post-trauma [24] and then vasogenic edema related to the severity of macrophage-rich inflammation with the expression of high levels of inflammatory cytokines and chemokines [18, 19] and focal injury to individual cortical

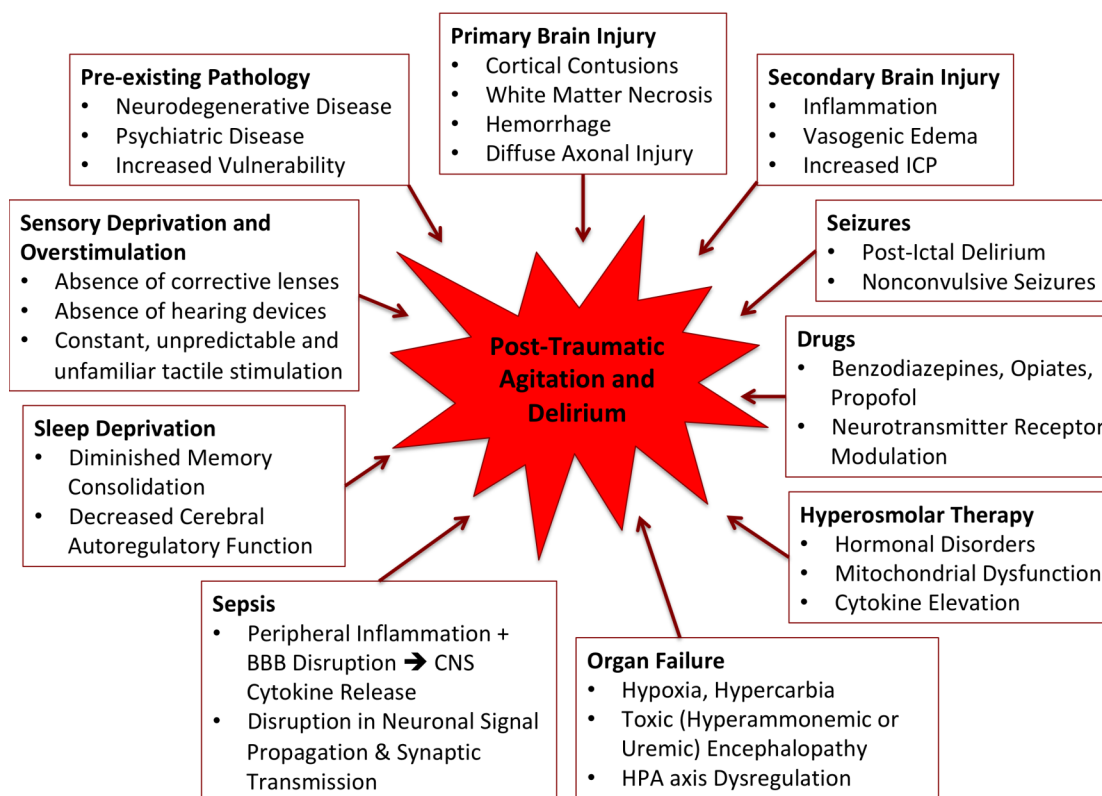


Fig. (1). Contributors to delirium in acute TBI. See text (sections 2.1-2.10) for detailed explanations. BBB: Blood-brain barrier; CNS: central nervous system; HPA: hypothalamic/pituitary/adrenal; ICP: intracranial pressure. (A higher resolution / colour version of this figure is available in the electronic copy of the article).

and subcortical brain structures supporting normal arousal, attention and cognition, increasing susceptibility to delirium.

2.2. Secondary Injury

Direct blunt force injury and shear injury to vascular structures result in epidural, subdural, intraparenchymal, and intraventricular hemorrhage. Ischemic infarction may also occur and is most often in association with carotid or vertebral artery dissection [25]. Like primary brain injury mechanisms, these may lead to delirium via diffuse mechanisms involving edema and inflammation, or via focal effects associated with compression or ischemic injury of brain structures involved in arousal, attention, and cognition.

Additionally, these same pathologies may result in increased intracranial pressure due to edematous or hematogenous infiltration of the intracranial compartment. The increase in intracranial pressure results in a decrease of cerebral perfusion pressure and, more importantly, cerebral blood flow, which may result in impaired levels of consciousness, manifesting as delirium or coma [26].

Secondary injury may also result from trauma-related neuroinflammation. Severe TBI can lead to an intense macrophage infiltration of necrotic areas with vasogenic edema building up in the surrounding brain due to disruptions in the blood-brain barrier (BBB) [18, 19]. This inflammatory process has been studied in detail and systematically in the spinal cord injury (SCI) rat model [18]. Its relevance to human TBI is related to high content of the white matter

in the spinal cord and very high content of the white matter and frequent involvement in the TBI. Post-SCI inflammation is fueled by and sustained for many weeks by the large quantity of damaged, disrupted myelin, resulting in the vicious cycle [18] with further destruction of the CNS tissue surrounding the areas of inflammation. High levels of inflammatory cytokines including IL-1 β , IL-6 and IFN- γ and chemokines coincide with the severity of phagocytizing, inflammatory, CD68+/CD163- macrophages infiltrating the initial injury [18, 27]. The severe inflammatory process contributes to the vascular damage and vasogenic edema in the surrounding CNS for a long time [18, 19]. The spinal cord reaction to injury and inflammation results in the formation of a cavity of injury (COI) where inflammatory infiltrate is sequestered and walled off by progressively severe astrogliosis implying an attempt of this CNS tissue reaction at restoration of homeostasis [18, 19, 28]. The pathogenesis of the COI forming after the TBI needs to be elucidated in detail in preclinical studies involving a model with a large brain with a high content of the subcortical white matter, such as in a pig since the rodent brain contains very little white matter and an injury to the hemisphere results in gray matter injury with much more limited consequences versus the white matter injury with serious pathologic implications in the TBI.

Macrophage infiltration of the COI coincides with the apparent movement of the extra edema fluid from the surrounding CNS via astrocytic syncytial systems with participation of aquaporin-4 (AQP-4) water channels [19, 29]. Thus the fluid and macrophage-containing COI serve as a potent

impediment for intra-neuronal signals and an insurmountable barrier for neuronal regrowth [30-32]. All of these pathologies; (1) necrosis, hemorrhage and edema caused by trauma, (2) severe, destructive and extraordinarily prolonged inflammation, (3) astroglial reaction resulting in the restriction of the inflammatory process to the COI and its inhibition and elimination therein [18, 32], (4) vasogenic edema sustained by inflammatory damage to BBB in the CNS surrounding the COI, (5) and astroglial reaction shunting excess edema fluid into the COI and external and internal brain surfaces [19, 33] play a crucial role in the pathologic mechanisms of post-traumatic brain dysfunction.

The mechanisms by which the observed neuroinflammatory cascade precipitates delirium have yet to be fully elucidated. Derangements in dopaminergic, serotonergic and cholinergic systems have been observed in TBI patients and may play an intermediary role [20]. Imbalances of dopamine, norepinephrine and serotonin are associated with cognitive dysfunction [34]. Hippocampal cholinergic neurons are essential for the maintenance of attention [35, 36]. Ionic shifts that may result from the abnormal presence of inflammatory mediators may lead to disruption of homeostatic control of normal neuronal firing processes [37].

2.3. Seizures

An estimated 9% of TBI patients develop seizures during the acute post-traumatic period, and this number increases to 27% in those with an injury severe enough to cause a depressed skull fracture [38, 39]. Convulsive seizures are typically associated with post-ictal delirium that may last minutes to hours after the convulsion. Nonconvulsive seizures are typically characterized by confusion and altered sensorium in association with repetitive neuronal discharges, as evidenced by electroencephalography (EEG). Approximately half of the seizures occurring during the acute post-traumatic period are nonconvulsive in nature [40]. Proposed mechanisms underlying post-ictal delirium are varied and include the imbalance of excitatory and inhibitory neurotransmission, exhaustion of metabolic processes mediating normal neuronal function, disruption of extracellular electrolyte balance (in particular K^+ and Ca^{++}), presence of reactive oxygen species, hypoperfusion, hypoxemia and blood-brain barrier damage [41].

2.4. Treatments

Many moderate to severe trauma patients require mechanical ventilation. Sedatives in association with this intervention, particularly benzodiazepines, are associated with increased risk and duration of delirium in critically ill patients [42-44]. The deliriogenic effects of these agents are likely due to their effect on neurotransmitters that appear to be critical to maintenance of arousal and conscious memory processing, in particular gamma-amino butyric acid (GABA), acetylcholine, dopamine and serotonin [45, 46]. Modulation of sleep physiology may represent a contributing mechanistic pathway [47].

Other drugs commonly used to treat TBI patients in the ICU may also cause altered mental status. Intravenous opioids have been explored as a means of sedation and pain

management during nursing interventions (e.g. suctioning for mechanical ventilation) but may contribute to delirium by inducing increases in intracranial pressure (ICP) and decreases in cerebral perfusion pressure (CPP) [48, 49]. Cephalosporins have historically been implicated in confusion or hallucinations in up to 25% of patients [50]. There are numerous reports of new-onset encephalopathy in the setting of administration of penicillins or fluoroquinolones [51, 52], although, in well-controlled cohorts with precise measures of delirium, these data have not been consistent and have been challenged [53]. Cyclobenzaprine, a centrally acting muscle relaxant widely used for pain and muscle stiffness, has been reported to induce psychosis in rare cases [54].

Perhaps as important as the influence of drugs administered as therapeutic interventions, withdrawal of pharmacologic and other chemical substances from the outpatient setting must be considered in the differential diagnosis of post-traumatic delirium. Chronic ingestion of opiates, benzodiazepines and/or alcohol is common among patients with TBI – approximately 45% of TBI patients endorse problems associated with drinking on the Short Michigan Alcoholism Screening Test [55], and approximately 35% endorse illicit drug use prior to hospitalization [56]. Benzodiazepine and alcohol withdrawal syndromes can manifest with fluctuating disturbances of attention and cognition, sometimes with hallucinations [57]. Opiate withdrawal may result in sympathetic arousal in association with hyperalgesia [58] and can manifest with agitated behavior, confused speech and sleeplessness [59]. Nicotine withdrawal is also associated with an increased risk of agitation in ICU patients [60].

2.5. Hyperosmolar Therapy and Dehydration

Hyperosmolar therapy with dehydration is commonly used to control increases in intracranial pressure that can occur in TBI patients. Yet dehydration may impair cognitive function and mental performance via hormonal disorders, mitochondrial dysfunction and brain cytokine elevation [61]. Severe dehydration following heat stress is associated with memory deficits and disorders of perception, even in healthy individuals [62]. Dehydration has also been recognized as an independent predictor of mortality following a diagnosis of delirium [63]. The most commonly utilized osmotic therapies in brain edema are based on two hyperosmotic medications: mannitol and hypertonic saline. It has been documented that hypernatremia following hyperosmotic treatment or treatment with hypertonic saline is neurotoxic and impair neuronal metabolisms with ATP reduction, which may contribute to cerebral dysfunction and delirium [64]. Interestingly, the same study did not show a similar neurotoxic effect with mannitol. Clinical observation confirmed that hypernatremia was an independent risk factor for sepsis-related encephalopathy, alteration of mental status, and higher mortality [65]. Of note, severe hypernatremia resulting from a critical neuronal injury is frequently observed in TBI patients. It needs to be pointed out that hyperosmotic therapies have been used since World War I, >100 years ago, and address only approximately 11% of the total excess edema evacuation in the cat model of TBI [33], leaving the remainder 87% of edema fluid evacuation via external (into the subarachnoid space), via internal (into cerebral ventri-

cles) [33, 66] and into the COI [19]. If similar paths for the evacuation of edema fluid from the post-TBI human brain are considered, and the source of vasogenic edema is related to the persistent severity of inflammation, the need for effective anti-inflammatory therapies resulting in inhibition of vasogenic edema [19] appears obvious in better management of brain edema.

2.6. Organ Failure

TBI patients are at increased risk for multiple systemic complications, including hypoxia due to neurogenic pulmonary edema and acute respiratory distress syndrome, catecholamine excess and autonomic nervous system or endocrine dysfunction due to dysregulation of the hypothalamic/pituitary/adrenal axis. Greater than 80% of admissions for severe TBI are complicated by cardiorespiratory failure during the ICU phase [67]. These conditions can lead to the widespread failure of neuronal metabolism due to hypoxemia and hypercarbia. Irregular adrenal release of norepinephrine can cause hyperarousal and disrupt attention and other cognitive processes mediated by the prefrontal cortex [68, 69]. Four to 23% of TBI admissions are complicated by acute kidney injury [70-72], which may result in hypernatremia or uremic encephalopathy, increasing morbidity and mortality in TBI patients [73]. Focal brain injury may also elicit rapid hepatic production of chemokines, amplifying the inflammatory response [74, 75]. The mechanisms by which these cause confusion and somnolence are incompletely understood, but osmotic edema and imbalances in excitatory and inhibitory neurotransmission may play a role [76].

2.7. Sepsis

According to the neuroinflammatory hypothesis of delirium development, inflammatory cytokines circulating in the periphery (e.g. in response to a secondarily acquired pneumonia or wound infection in a TBI patient) may trigger the release of inflammatory mediators by brain vascular endothelial cells and microglia. Cytokines associated with delirium in sepsis include TNF- α , IL-1 β , TGF- β and MCP-1 [77]. Levels of IL-6 and plasminogen activating inhibitor-1 (PAI-1) are associated with a longer duration of delirium in patients with dementia [78]. The inflammatory mediators may directly impair neuronal function by disrupting the carefully balanced milieu that allows for axonal signal propagation and synaptic transmission. They may also activate microglial cells that have been primed by aging or neurodegenerative disease [79]. Mechanisms by which systemic inflammation may lead to delirium are discussed in section 2.2 above.

2.8. Sleep Deprivation

Critically ill patients suffer from severe sleep fragmentation and abnormal circadian rhythms. Nearly 100% of mechanically ventilated patients experience atypical sleep patterns as measured using polysomnograms (PSG) and electroencephalography (EEG) [80]. These disruptions are not surprising given the acute nature of the ICU environment with its around-the-clock assessments and life-saving interventions. Constant environmental noise and persistent unfamiliar tactile stimulation (e.g. by ventilator tubing or wrist re-

straints) worsen sleep by causing more frequent arousals [81]. Sleep is an important part of the memory consolidation process, [82], and interventions to improve sleep quality in the ICU result in reduced risk and duration of delirium [83, 84]. Additionally, sedative-hypnotic agents can modulate the sleep pathway and contribute to delirium [47], although they also may contribute to delirium prevention [85]. The mechanisms by which sleep deprivation may lead to or exacerbate delirium in TBI patients are varied. Perturbation of sleep homeostasis is often associated with an increase in hypothalamic-pituitary-adrenal axis activity, which increases circulating cortisol levels [86] and may reinforce an already hyper sympathetic state by increasing metabolic demand and impeding essential repair processes [87, 88].

2.9. Sensory Deprivation or Overstimulation

Elderly patients with a history of vision or hearing loss are twice as likely to develop new and persistent disability after critical illness as those with intact sensory abilities [89]. This is postulated to be mediated by delirium, given that hearing and vision impairment both confer increased risk of delirium [90] and protocolized interventions to use glasses and audiophones decrease its risk [91].

2.10. Contribution of Preexisting Pathology

Premorbid dementia is associated with a 2 to 4-fold increased odds of ICU delirium [90, 92]. Other neurodegenerative diseases such as Parkinson's Disease [93], as well as preexisting psychiatric disease (in particular depression), also increase the risk of delirium [90]. Traumatic brain injury itself causes a cascade of neurodegenerative and inflammatory changes, and re-injury in patients with a prior TBI can be expected to predispose to ICU delirium or coma, though there is a paucity of data examining this relationship [94].

3. MANIFESTATIONS OF DELIRIUM IN TRAUMATIC BRAIN INJURY

Delirium can be classified into subtypes according to the nature of the accompanying motor manifestations: hyperactive, hypoactive or mixed [95]. Patients with hypoactive delirium are typically lethargic and demonstrate reduced motor activity. These patients are often mistaken for sleeping, yet they are difficult to arouse and, when they do arouse, may appear disinterested in the world around them. In contrast, patients with hyperactive delirium may show increased wakefulness and are often hyper-alert, agitated and restless. Hyperactive delirium may also present with extreme expressions of fear, anxiety or psychotic symptoms such as hallucinations, illusions and delusions. Patients with mixed delirium have symptoms of both hypoactive and hyperactive delirium that change over the course of the disease. Rarely, delirium may occur with normal levels of arousal. Although hypoactive delirium is the most easily overlooked, this form combined with mixed delirium are the most common presentations in the ICU, accounting for 66-90% of cases [95, 96].

Hypoactive delirium tends to be more frequent in women and in older adults [97]. Though normoactive delirium appears more clinically benign, among those over 65 years of age it portends a worse prognosis, including increased mor-

tality, worse cognition and poorer functional status at 6 months after hospitalization [98, 99].

4. NEUROIMAGING FINDINGS IN DELIRIUM AND ACUTE TBI

Trauma patients presenting with altered neurologic function and/or mechanism should be suspected of TBI and undergo non-contrast computed tomography (CT) of the brain [100]. Common CT findings on presentation include skull fractures, extra-axial (epidural, subdural and subarachnoid) or intra-axial (intraparenchymal or intraventricular) hemorrhages, contusions of the brain cortex and microhemorrhages in multiple white matter structures indicating diffuse axonal injury [101]. Foreign bodies causing penetrating injury may also be localized. CT findings may be normal in mild TBI and in ICU delirium.

New delirium, coma, or other neurologic symptoms during the subacute phase should prompt repeat CT imaging. The primary purpose is to rule out new hemorrhage, cerebral edema, inflammatory areas and herniation. Magnetic Resonance Imaging (MRI) of the brain can be used when there are persistent neurologic deficits in the face of a normal CT. Acutely, MRI can demonstrate early signs of ischemic stroke, delineate specific brain structures (e.g. brainstem) involved in traumatic injury and detect microvascular hemorrhage. MRI provides a more detailed visualization of intracranial pathology and has higher sensitivity for detection of traumatic axonal white matter injuries, brainstem injuries, non-hemorrhagic cortical contusions, and epidural or subdural hematomas [102, 103], but may have limited prognostic potential and rarely changes ICU management [104]. The systematic use of MRI in patients with TBI resulting in severe inflammation and vasogenic edema should allow for the useful monitoring of these pathologic processes and in precise gaging of the inhibition and elimination of inflammation and of vasogenic edema by future effective anti-inflammatory therapies. MRI scans performed months to years after the injury may show focal areas of encephalomalacia (indicating structural remodeling after an injury to the brain parenchyma) and in approximately 80% of cases, the persistence of traumatic microbleeds on T2-weighted imaging [105]. All of these structural anomalies may contribute to delirium pathogenesis.

5. NEUROPHYSIOLOGIC FINDINGS IN DELIRIUM AND ACUTE TBI

In the acute phase, continuous EEG may be considered in severe TBI to rule out recurrent seizures or nonconvulsive status epilepticus [13] and should be considered in the case of delirium. The most common EEG findings in delirium include disruption of normal signal patterns, including slowing of the posterior dominant rhythm, generalized irregular delta (0.5-4 Hz) or theta (4-7 Hz) activity, and decreased amplitude [106]. Triphasic waves [107] may also be present. Focal hemorrhages or contusions may be manifest as focal slowing recorded from the overlying scalp or by frontal intermittent rhythmic delta activity [108]. A study of 49 patients with post-traumatic confusion found increased delta and decreased alpha (8-12 Hz) activity associated with increasing severity of confusion [109]. These findings are pos-

tulated to reflect focal or global neuronal dysfunction as a result of metabolic insufficiency – a mismatch between the cerebral metabolic requirement and the nutrient availability to support cerebral metabolism [110]. In patients with post-traumatic delirium due to nonconvulsive seizures, EEG findings may include intermittent epileptiform spikes or sharp waves, periodic discharges, lateralized rhythmic delta activity (LRDA) or frank seizures [111-113].

In patients with severe TBI, the utility of electrocorticography (ECoG) is an active area of research. ECoG may detect cortical spreading depressions, which have been associated with secondary brain injury and worse clinical outcomes [114].

6. MANAGEMENT PRINCIPLES

Altered mental status at presentation or during hospitalization for trauma is a potential neurologic emergency. Acute changes in cognition or level of consciousness raise concern for intracranial hemorrhage (ICH). ICH can be classified as epidural, subdural, subarachnoid, intraparenchymal or intraventricular depending on its predominant location within the intracranial space. Other frequent causes of new onset delirium in trauma patients include cerebral edema (which can cause increased intracranial pressure and compression of vital structures), as well as seizure. While the latter may present with violent convulsive shaking and jerking activity, hypersalivation, incontinence and loss of awareness, there has been growing awareness of non-convulsive seizures and non-convulsive status epilepticus. The clinical manifestations for these more “bland” phenomena may include altered sensorium, confusion or subtle intermittent twitching of one side of the face or a single extremity.

In the absence of organic causes of delirium in TBI patients (intracranial mass lesions, increased intracranial pressure, intracranial or systemic infection or seizure), delirium management that has been established as effective across critically ill populations must be implemented.

6.1. Pharmacologic Management of Post-traumatic Delirium: Current State of the Evidence

Several drug therapies have been investigated for the prevention and treatment of delirium after TBI (See Table 1 for summary). The following subsections discuss medication options and the current state of literature about them.

6.1.1. Benzodiazepines

The anxiolytic, sedative and tranquilizing effects of benzodiazepines have been acknowledged since Leo Sternbach's discovery of chlordiazepoxide in the mid-1950s [115]. These effects are mediated by positive allosteric modulation of the gamma-aminobutyric acid (GABA) type A receptor [116] and make this class of medications a logical candidate for behavioral agitation in association with traumatic brain injury. In a 1994 survey of physicians treating brain injury patients, 30-35% reported using benzodiazepines as the first, second, or third-line agent for agitation [117], and a subsequent investigation of 182 consecutive moderate to severe TBI survivors managed in a level I trauma unit found that benzodiazepines were administered in 67% of cases [118].

Table 1. Summary of major drug classes investigated for management of post-traumatic delirium or agitation. AChE: acetylcholinesterase; AVP: Avenir Pharmaceuticals; CBZ: carbamazepine; D2: dopamine type-2 receptor; GABA-A: gamma-aminobutyric acid type-A receptor; ROS: reactive oxygen species; UTI: urinary tract infection.

Drug Class	Possible Mechanism(s)	Potential Benefits	Risks/Cautions	Recommended?
Beta-Blockers (e.g. propranolol, pindolol)	Beta-adrenergic receptor antagonism	Modulation of somatic symptoms related to sympathetic drive	Hypotension Bradycardia	Yes
Antiseizure drugs (valproate, carbamazepine)	Inhibition of arachidonic acid neurotransmission	Mood stabilization Improved behavioral disruption and confusion	Worse neurobehavioral performance on medication (CBZ)	Yes
Psychostimulants (methylphenidate, donepezil, AVP-786)	Multiple	Improved attention, memory Improved disinhibition	Decreased appetite (methylphenidate) Increased bowel frequency (donepezil) Falls, UTI, Somnolence (AVP-786)	Not currently
Flavonoids (e.g. quercetin, xanthohumol)	AChE inhibition Decreased concentration of intracellular ROS	Improved behavior Possible neuroprotective effect	Animal studies only	Not currently
Antipsychotics (e.g. haloperidol, ziprasidone)	D2 receptor antagonism	Improve psychosis Sedation	Longer duration of post-traumatic agitation Extrapyramidal symptoms Worse cognitive outcomes	No
Anti-inflammatory drugs and Immunomodulators (e.g. meloxicam, methylprednisolone)	Modulation of inflammatory signal cascade	Improved behavior	Increased mortality	No
Benzodiazepines (e.g. lorazepam, alprazolam)	GABA-A agonism	Sedation Anxiolysis	Paradoxical excitation Slowed neuronal repair processes Worse TBI outcomes	No

Increasing evidence that this treatment may produce a paradoxical agitation impede neuronal repair processes and worsen outcomes after TBI has been associated with a decrease in popularity of this drug class among TBI management specialists [119-123]. A systematic review conducted by the French High Authority for Health (HAS) in collaboration with the French Society of Physical and Rehabilitation Medicine (SOFMER) concluded that benzodiazepine could be used only in emergency situations and where anxiety is the predominant symptom [124]. The Society of Critical Care Medicine recommends the use of propofol or dexmedetomidine in lieu of benzodiazepines for sedation of mechanically ventilated, critically ill adults in both medical and surgical intensive care units [125].

6.1.2. Beta-blockers

A 2006 systematic Cochrane review found that the best evidence for pharmacologic management of agitation or ag-

gression after traumatic brain injury supported use of beta-blockers [126]. Since TBI is associated with a hyperadrenergic state that may induce hypermetabolism and increase cerebral oxygen demands [127], beta-blockers are commonly used for reducing hyperadrenergic activity in post-TBI patients [128]. A recent meta-analysis suggests a reduction in the odds of in-hospital mortality by 65% in patients receiving beta-blockers [129]. Regarding post-traumatic agitation and delirium specifically, a study involving 10 TBI patients in a double-blind, placebo-controlled, cross-over design resulted in a significant reduction of assault episodes with pindolol [130]. Propranolol, a lipophilic, nonselective beta-receptor antagonist with CNS effects [131], was evaluated in a single placebo-controlled trial of 21 patients and had a significant decrease in intensity of agitation without significant effect on the frequency of behavioral outbursts [132]. Propofol may also decrease mortality [128] after TBI. Propranolol crosses the BBB and disrupts noradrenergic output from the locus ceruleus to the lateral amygdala [133, 134], although it

is suggested that the anxiolytic effects of beta-blockers are primarily mediated by the improvement of somatic symptoms related to modulation of sympathetic drive [135, 136].

6.1.3. Antiseizure Drugs

Antiseizure drugs such as valproate and carbamazepine have long been recognized as mood stabilizers [137, 138] and may have some efficacy in controlling post-traumatic delirium. Valproate and carbamazepine are postulated to exert their effect by downregulating turnover of arachidonic acid (AA) in brain phospholipids, prostaglandin E2 formation, and/or expression of AA-cascade enzymes, thus inhibiting AA neurotransmission via dopaminergic and glutamatergic receptors [139-141]. There may also be a synergistic effect between carbamazepine and buspirone, a non-sedating azaspirodecanedione anxiolytic with presynaptic dopamine receptor modulating, 5HT-1a receptor agonistic and norepinephrine agonistic properties [142, 143]. This combination was reported to improve behavioral disruption and confusion in a small case series of patients with traumatic brain injury [144]. TBI patients taking carbamazepine temporarily showed a substantial improvement in neurocognitive test scores after drug discontinuation [145], suggesting this drug should not be continued indefinitely. In a separate randomized trial evaluating neuropsychological effects of valproate, this drug did not appear to have significant positive or negative effects on neurocognitive performance [146]. The HAS/SOFMER Guidelines recommend valproate and carbamazepine as first line agents for agitation, aggressiveness, anger and irritability after TBI [124]. This recommendation was based on results of four trials each including between 4 and 20 participants with TBI. Few randomized controlled trials exist evaluating antiseizure drugs in larger populations, however, and further investigation is needed [20].

6.1.4. Antipsychotics

Antipsychotic medications have been used since the 1950s to diminish anxiety, agitation and confusion in association with psychosis [147] and, for decades, were thought to be the drugs of choice for delirium in critically ill patients [148, 149]. In 1978 the use of intravenous haloperidol was reported in a series of 15 delirious patients during recovery from cardiac surgery [150] and this class of medications became the mainstay of treatment for delirium and agitation in the critically ill, both with and without head trauma [151, 152]. The next several decades saw an increasing reliance on antipsychotic medications for this purpose. In 2002, the SCCM guidelines for use of sedatives and analgesics in ICU recommended haloperidol as the preferred agent for the treatment of delirium in critically ill patients [149], and the use of antipsychotics in TBI patients was commonplace: a query of 195 patients in the national TBI Model Systems Database found that 26.7% received antipsychotics within 7 days of injury [153].

First-generation antipsychotics such as haloperidol and chlorpromazine bind to dopamine D2 receptors with high affinity, and their affinity to this receptor correlates well with therapeutic doses [154]. Thus dopaminergic antagonism is postulated to be the primary mechanism of their antipsy-

chotic effect [155], although it is thought likely mediated by indirect effects in a signaling cascade between

D2 receptors and D1 receptors [156]. Both first generation and second-generation antipsychotics such as ziprasidone, risperidone, aripiprazole, olanzapine and quetiapine bind to a host of other neurotransmitter systems as well. Atypical antipsychotics, in particular, have some additional affinity for serotonin (5-HT) type 2A receptors, and this balance between serotonergic and dopaminergic pathways may explain the lower risk of extrapyramidal symptoms and additional anxiolytic effect of these medications [157, 158].

A recent large, randomized, placebo-controlled trial comparing haloperidol and ziprasidone failed to show any difference in delirium- and coma-free days between either of these drugs and placebo [159]. Although smaller prospective studies suggest the potential efficacy of atypical antipsychotics specifically for post-traumatic agitation (hyperactive delirium) [160], these effects have been overshadowed by concerns of worsened cognitive outcomes. Several animal studies demonstrate impairments in motor and cognitive recovery after TBI with the use of haloperidol or risperidone [161-163]. Repeated administration of these agents is detrimental to motor and cognitive recovery in preclinical models of TBI [164]. Among 195 patients from a single level 1 trauma center in the national TBI Model Systems database, the duration of post-traumatic amnesia was longer in those who received antipsychotics within the first 7 days compared to those who did not (mean 19.6 days vs. 12.3 days, $p=0.013$) [153]. A retrospective study of 182 moderate to severe TBI survivors found that antipsychotics were associated with longer periods of post-traumatic agitation and a trend toward worse cognitive scores at the time of discharge to rehabilitation [118]. The study did not specify which individual antipsychotics were used.

These risks to cognitive function are superimposed on a risk of developing neuroleptic malignant syndrome among TBI patients [165], which has further discouraged the use of antipsychotics in TBI patients. The current recommendations on the management of post-traumatic delirium from the International Panel on Cognition (INCOG) are thus to minimize the use of this class of medications [166]. The 2014 HAS/SOFMER recommends a non-pharmacological approach or an alternative to neuroleptics but recognizes the potential for use of these medications in the case of emergency or acute aggressiveness [124]. The Society for Critical Care Medicine also suggests against the use of haloperidol or atypical antipsychotics to prevent delirium or treat subsyndromal delirium in critically ill adults [125]. These guidelines also suggest not routinely using haloperidol or atypical antipsychotics to treat delirium. Notably, olanzapine has not been demonstrated to impair cognition after TBI and is currently the subject of a randomized controlled trial for post-traumatic agitation [167].

6.1.5. Psychostimulants

The psychostimulants methylphenidate (a presynaptic norepinephrine and dopamine reuptake inhibitor [168]) and donepezil (a reversible noncompetitive acetylcholinesterase inhibitor [169]), have each been shown in randomized con-

trolled trials to have clinically significant positive effects on attention and other cognitive functions impaired in delirium [170, 171]. In small trials, the adverse effects identified with these medications included poor appetite with methylphenidate [172] and increased bowel frequency and incontinence with donepezil [170].

AVP-786, a combination of deudextromethorphan hydrobromide and quinidine sulfate, is currently the subject of a randomized controlled trial for the treatment of neurobehavioral disinhibition after TBI [173]. The active agent in this drug is the dextromethorphan moiety, which exerts several effects on the CNS [174]:

- low-affinity antagonism of the NMDA receptor.
- sigma-1 receptor agonism.
- serotonin and norepinephrine reuptake inhibition.
- nicotinic alpha-3-beta-4 receptor antagonism.

AVP -786 is formulated by deuteration of dextromethorphan and combination of the resultant drug with quinidine to reduce first-pass cleavage by the cytochrome P450 system and increase CNS bioavailability [175, 176].

6.1.6. Anti-inflammatory Drugs and Immunomodulators

Given the prominent role of the inflammatory cascade in the pathogenesis of TBI and also in the hypothesized pathogenesis of delirium, the utility of anti-inflammatory agents has been considered. Non-steroidal anti-inflammatory drugs (NSAIDs) such as meloxicam and carprofen [177-179], immunomodulators such as etanercept and minocycline [180, 181], and the anti-oxidant N-acetyl cysteine [182] successfully modulate inflammatory biomarkers and in some cases behavioral measures in animal models of TBI [183]. The impact of these agents on delirium and cognitive outcomes in TBI in humans has not been established.

Because the Corticosteroid Randomization After Significant Head Injury (CRASH) trial demonstrated increased 6-month mortality in TBI patients receiving methylprednisolone infusion compared to a placebo group (25.7% versus 22.3%, RR 1.15, 95%CI 1.07-1.24, p=0.0001) [184], the use of steroids is not recommended in this patient population [185].

6.1.7. Flavonoids

Recently, different extracts from natural components have been suggested to prevent or treat neuroinflammatory responses following different pathologies. Quercetin, a member of the flavonoid family, efficiently protects neuronal cells against H₂O₂ toxicity [186]. Its administration decreases concentration of intracellular reactive oxygen species and improves mitochondrial function, which can attenuate the neurodegeneration process, memory loss and cognitive impairment. Experimental study confirms that repeated administration of quercetin significantly improves memory, learning acquisition and cognitive function [187]. The same study documented a similar effect of naringenin, another flavonoid. Quercetin and naringenin also inhibit the activity of acetylcholinesterase and improve cholinergic neurotrans-

mission [187]. Of note, disorders in cholinergic neurotransmission are considered as important pathomechanisms for delirium, and the elevated acetylcholinesterase activity was associated with hypoactive delirium in cardiac surgery patients [188, 189].

The neuroprotective effect of flavonoids depends on their ability to penetrate the BBB. Only a few flavonoids have been able to cross the BBB [190]. Some of them also reduce raised BBB permeability following TBI, which reduces brain edema and neuroinflammatory response [191, 192]. Experimental studies have shown that Xanthohumol, a natural flavonoid extracted from hops, acts not only as neuroprotectant, but also stimulates neuroregenerative medications [192-194]. These compounds show high promise as neuroprotectants in CNS trauma and clinical investigations will be important to determine their effect in post-traumatic delirium.

6.2. The ICU Liberation Bundle

As we await clearer guidance on pharmacologic interventions appropriate for post-traumatic delirium, nonpharmacologic interventions have been the cornerstone of delirium prevention and treatment [195]. Interventions include promoting regular sleep-wake cycles, avoiding sensory overstimulation and regular reorientation. The recommendations set forth by the INCOG panel provide more specific strategies, including avoiding restraints, evaluating the impact of visitors and iatrogenic interventions that may exacerbate agitation, and establishing consistency among staff to promote familiarity [166]. Such interventions have been refined over the decades and have become standard of care for critically ill patients in ICUs worldwide. This approach can be summarized in the ICU Liberation Bundle, commonly referred to by the mnemonic “ABCDEF Bundle” (Fig. 2). The components of this are described in the subsections that follow:

6.2.1. A: Assess, Prevent and Manage Pain

TBI patients experience pain at rest and perhaps more so with routine procedures. Pain that is inadequately treated can result in delirium in addition to several other complications. Both behavioral and physiologic indicators of pain during nociceptive procedures must be observed, yet this may be challenging in unconscious mechanically ventilated patients [196, 197]. Pain should be monitored routinely in all adult ICU patients. This can be done by self-report if the patient is awake and communicative or by using a validated behavioral pain scale [198] in those who are unable to effectively communicate pain. The use of behavioral pain scales dedicated to non-verbal patients, namely the Behavioral Pain Scale (BPS) and the Critical Care Pain Observation Tool (CPOT) should be promoted [199, 200].

Optimal pain management may be extremely challenging in TBI patients who are often deeply sedated, receive neuromuscular blocking medications (NMB) and may suffer from additional injuries. Medical, nursing and physiotherapy teams should make all the possible efforts to ensure pain management is optimal and avoid extended periods of high-dose intravenous opioid infusions.



ICU Liberation: ABCDEF Bundle



Symptoms <small>Pain, Agitation, Delirium Guidelines</small>	Monitoring <small>Tools</small>	Care <small>ABCDEF Bundle</small>	Done
Pain	Critical-Care Pain Observation Tool (CPOT) NRS Numeric Rating Scale BPS Behavioral Pain Scale	A: Assess, Prevent and Manage Pain	<input type="checkbox"/>
Agitation	Richmond Agitation-Sedation Scale (RASS) Sedation-Agitation Scale (SAS)	B: Both Spontaneous Awakening Trials (SAT) and Spontaneous Breathing Trials (SBT) C: Choice of Analgesia and Sedation	<input type="checkbox"/> <input type="checkbox"/>
Delirium	Confusion Assessment Method for the Intensive Care Unit (CAM-ICU) Intensive Care Delirium Screening Checklist (ICDSC)	D: Delirium: Assess, Prevent and Manage E: Early Mobility and Exercise F: Family Engagement and Empowerment	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>

Fig. (2). ICU liberation schematic. This schematic depicts symptoms, monitoring tools, and the ABCDEF rounding checklist. From Ely, EW. The ABCDEF Bundle: Science and Philosophy of How ICU Liberation Serves Patients and Families. *Critical Care Medicine* 45(2): 321-330. Used with permission from Wolters Kluwer Health, Inc.

6.2.2. B: Both SAT and SBT

A spontaneous awakening trial (SAT) is a protocolized pause of intravenous narcotics and sedatives for assessment of level of consciousness. The drugs are restarted at half the prior dose when appropriate. A spontaneous breathing trial (SBT) is a protocolized period of minimal ventilator support, with the goal of assessing ongoing pulmonary ventilator requirements. A randomized, controlled trial comparing daily spontaneous breathing trials (SBTs) to the standard of care in mechanically ventilated patients revealed that those receiving SBTs had a shorter duration of mechanical ventilation (4.5 days vs. 6 days, $p = 0.003$). There were also fewer ventilator-related complications and lower ICU costs of care in the intervention arm [201]. Another randomized controlled trial comparing a daily SAT and SBT protocol against daily SBT with routine sedation found that patients on the SAT plus SBT protocol spent more days breathing without assistance and had shorter ICU lengths of stay. Patients receiving daily SAT were also less likely to die during the 12-month follow-up period. Rates of reintubation were similar in the two groups [202]. Daily consideration of SAT and SBT is a key part of the timely cessation of mechanical ventilation and leads to improved outcomes in the overall critically ill population. Studies comparing approaches specifically in TBI patients are currently lacking. The Extubation strategies in Neuro-Intensive care unit patients and associations with

Outcomes (ENIO) international observational study will examine ventilator liberation and tracheostomy practices in such patients [203].

6.2.3. C: Choice of Analgesia and Sedation

Effective management of pain, anxiety and delirium is an important objective in the ICU, particularly in brain injury patients in whom these symptoms may contribute to increased intracranial pressure. Management should be based on clearly established, patient-oriented goals and standardized assessment measures. There are several validated measures published for assessment of sedation level in the ICU, including the Richmond Agitation-Sedation Scale (RASS) and the Riker Sedation-Agitation Scale (RSAS).

The most effective medication and titration protocol for sedation and analgesia has yet to be elucidated and may differ depending on the clinical context and patient characteristics. The MENDS randomized, controlled trial compared the benzodiazepine lorazepam and the alpha-2 adrenoreceptor agonist dexmedetomidine for sustained sedation in mechanically ventilated patients and found more days alive without delirium or coma (median 7.0 versus 3.0 days, $p=0.01$) in the dexmedetomidine arm. Costs of care were similar between the two groups [204]. The MENDS2 study will compare dexmedetomidine and propofol in septic patients on mechanical ventilation. Results from that study are pending as

of the preparation of this manuscript. Studies examining the differential propensity of various sedation regimens to alter the risk of post-traumatic delirium are currently lacking.

Patients treated for moderate or severe TBI commonly require pharmacologic sedation for maximal reduction of increased ICP in response to sensory stimulation. Current guidelines recommend the use of barbiturates and/or propofol to control elevated, refractory ICP [185]. Yet, it has been well recognized that intravenous sedative medications influence the risk for delirium. Sedation with dexmedetomidine significantly reduces the risk for delirium compared to benzodiazepines in mechanically ventilated patients [204, 205], and compared to morphine in post-cardiac surgery patients [206]. Dexmedetomidine attenuates sepsis-induced hippocampal microglial activation [207]. The use of dexmedetomidine as adjuvant sedation to propofol infusion may better reduce neuroinflammatory response because these medications affect neuroinflammation through different mechanisms [207]. In a mouse model of TBI, treatment with dexmedetomidine attenuates early neurological dysfunction and BBB damage, reduces neutrophil infiltration, microglial activation, and pro-inflammatory mediator secretion, and reduces cellular apoptosis [208]. Interestingly, a clinical study has shown a significantly lower incidence of delirium after seizures induced by electroconvulsive therapy in patients premedicated with dexmedetomidine [209]. Although a meta-analysis of nine studies evaluating dexmedetomidine as a sedative and analgesic agent in critically ill adult patients failed to find a statistically significant difference among populations, the prevalence of delirium was lower in the dexmedetomidine group [210, 211] and this drug may prove useful in the prevention of delirium among TBI patients.

6.2.4. D: Delirium: Assess, Prevent and Manage

Monitoring for early identification and risk factor modification is a key component of delirium management. As indicated above, the most widely used tool for delirium assessment in the ICU is the Confusion Assessment Method for the ICU (CAM-ICU) [10]. This easy-to-administer bedside tool evaluates patients in four key domains: acute onset of mental status change or fluctuating course, inattention, disorganized thinking and altered level of consciousness. Among seven prospective cohort studies and a total of 1,173 patients, delirium was assessed in neurocritically ill patients using validated delirium tools after considering primary neurologic diagnoses and associated complications, finding a pooled prevalence rate of 12-43%. When able to compare against a common reference standard, Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, the test characteristics showed a sensitivity of 62-76%, specificity of 74-98%, positive predictive value of 63-91%, negative predictive value of 70-94%, and reliability kappa of 0.64-0.94 [212]. The Intensive Care Delirium Screening Checklist (ICDSC) is another widely accepted delirium screening tool [11]. The ICDSC is comprised of eight items: altered level of consciousness, inattention, hallucination/delusions/psychosis, psychomotor agitation or retardation, inappropriate speech or mood, sleep wake/cycle disturbance and symptom fluctuation. Its pooled sensitivity and specificity in the general ICU population are 74% and 82%, respectively [213].

Among four studies reporting multivariable analyses, delirium in neurocritically ill patients was associated with increased hospital length of stay (3 studies) and ICU length of stay (1 study), as well as worse functional independence (1 study) and cognition (2 studies), but not survival [212]. It is important to assess patients regularly to reduce the risk of overlooking hypoactive delirium, regardless of whether they are receiving intravenous sedatives. Spontaneous awakening trials present an optimal opportunity to perform this assessment [214].

Once hemorrhage, stroke, increased ICP and seizures have been ruled out, management of delirium entails revisiting primary prevention measures, including reorientation, an appropriate sleep environment, and adequate pain management. These interventions are important even in patients whose delirium is in association with sepsis, sedative effect, hypoxia or metabolic compromise. Since the duration of delirium predicts worse long-term cognition and mortality [215], these nonpharmacologic measures to limit its duration can be expected to improve patient outcomes.

6.2.5. E: Early Mobility and Exercise

There is a range of activities from passive range of motion to ambulation with the assistance that can be implemented as part of an early mobility program. Such programs are safe and feasible in critically ill patients and result in fewer days of delirium, shorter duration of mechanical ventilation, shorter ICU length of stay and shorter hospital length of stay. Any member of the care team can perform early mobility activities, although the appropriate level of activity should be determined based on the patient's level of sedation. Early mobilization during spontaneous awakening trials improved odds of return to independent functional status by discharge (OR 2.7, 95% CI 1.2-6.1) in a series of critically ill adults on mechanical ventilation [216]. Feasibility of early combined cognitive and physical therapy has also been demonstrated in a similar population [217] as well as in pediatric TBI patients [218], and outcomes are currently under study. These findings may be of particular salience in the TBI population given the increased risk for adverse cognitive outcomes compared to the general ICU population.

6.2.6. F: Family Engagement and Empowerment

Encouraging family members to participate actively inpatient care can result in improved ICU team performance and communication, reveal important insights to the patient condition and keep providers focused on the most salient goals of care for each patient. Family engagement and empowerment may also lead to early identification of and reduction in the burden of ICU-related psychological and emotional stress among family members (a harbinger of post-intensive care syndrome for the family, or PICS-F) [219]. Key elements of strategic communication with families include using simplified language, focusing on concrete issues and avoiding the presentation of large boluses of information without adequate time for family members to process. A recent systematic review and meta-analysis of protocolized family support interventions found that these interventions reduce ICU length of stay but do not adversely affect mortality [220].

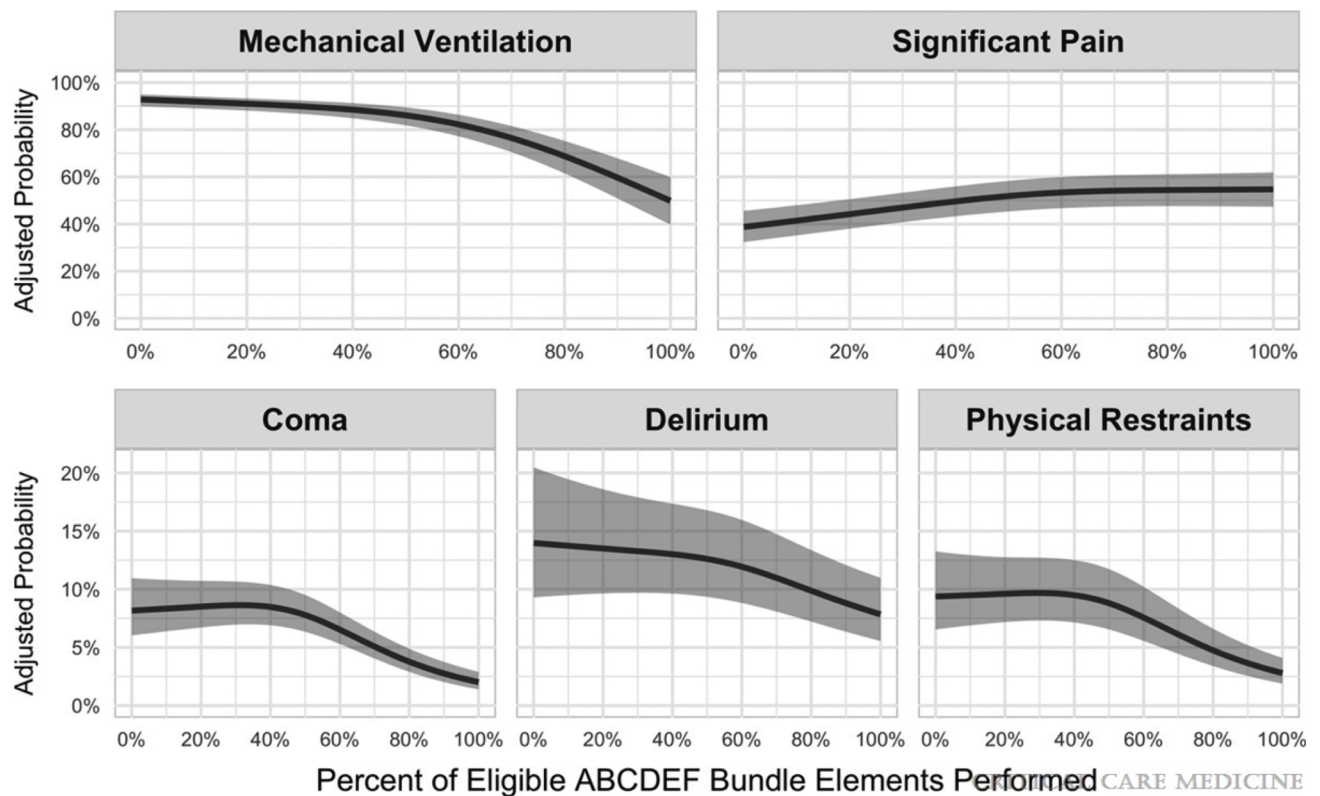


Fig. (3). Association between performance of the ABCDEF Bundle and risk of symptom-related outcomes the following day from the ICU Liberation study, a multicenter study of 15,226 adults in 68 ICUs. X axes represent proportion of eligible ABCDEF bundle elements performed on a given day, and Y axes represent adjusted probability of a patient experiencing a given symptom-related outcome on the following day. For example, complete bundle performance was associated with an adjusted odds of 0.60 (95%CI 0.49-0.72) of suffering delirium the following day and an adjusted odds of 0.35 (95%CI 0.22-0.56) of suffering coma the following day. From Pun et al., Caring for Critically Ill Patients with the ABCDEF Bundle: Results of the ICU Liberation Collaborative in Over 15,000 Adults. *Critical Care Medicine* 47(1):3-14. Used with permission from Wolters Kluwer Health, Inc.

6.2.7. Implementation Challenges

Improvements in compliance with the ICU Liberation bundle are associated with a reduction in mortality and improvement in a number of patient-oriented symptoms including delirium (Fig. 3) [221, 222]. Yet systematic implementation of this bundle, including delirium screening, is lacking in many ICUs [223-226] due to a number of barriers. Nurses may report that delirium is difficult to evaluate in intubated patients [225, 227-229] and some feel that sedated patients could not be assessed [225, 228]. Importantly, the CAM-ICU was specifically designed to assess nonverbal ICU patients receiving mechanical ventilation, and the current CAM-ICU training manual [230] indicates that the only condition incompatible with CAM-ICU assessment is unresponsiveness to verbal stimulation (RASS < -3) irrespective of sedative use.

Some clinicians suggest that delirium can be identified without an assessment tool [227, 231]. Yet without a validated screening tool, nurses and intensivists only recognized 25-35% of delirious days [232, 233]. Missed diagnosis may lead to lack of treatment, whereas false positives due to lack of objectivity may expose patients to unnecessary pharmacological therapy despite its unproven efficacy [234] and safety risks [235, 236].

It may be argued that the TBI population represents a unique group of critically ill patients and the focal neurologic deficits in this population may require special delirium evaluation and prevention tools. Indeed, there is limited literature on the best methodologies for implementation of the ICU Liberation bundle, specifically in the trauma ICU population [237]. Importantly, both the CAM-ICU and the ICDS-C have good sensitivity and specificity for evaluating delirium in TBI patients [238, 239].

More broadly, the implementation of the ABCDEF Bundle as a whole can substantially improve outcomes, including reducing the odds of developing delirium and reducing the chances of requiring mechanical ventilation in non-ventilated [221, 240]. Barriers to implementing the ABCDEF as a bundle are similar to the ones encountered when using a delirium assessment tool. Some are related to the patient, including safety concerns in terms of hemodynamic stability or decreased levels of cooperation [241]. Other barriers include lack of knowledge about the benefits and efficacy of the bundle, preference for autonomy and perception of increased workload [241-243]. Finally, there are barriers related to the structure of the ICU, including culture and organization, teamwork, physical environment, lack of resources, and inadequate management/leadership [241, 242, 244]. Importantly, implementation of these recommenda-

tions can reduce provider workload by optimizing patient interactions and minimizing requirements for ICU-level care.

6.3. Treatment and Prevention of Potential Contributing Factors

Optimal treatment of delirium associated with traumatic brain injury is determined by the etiology. Thus, the management necessarily starts with a neurologic assessment to include neurologic examination, brain imaging and consideration of electroencephalography (EEG). The following subsections describe interventions appropriate for each potential etiology of delirium in this population.

6.3.1. Operative Management of Intracranial Hemorrhages

Patients with hemorrhages evident on brain computed tomography (CT) imaging may benefit from surgical intervention, and recommendations vary depending on the brain compartment in which the hemorrhage occurs. Evacuation is recommended for epidural hematomas (EDH) greater than 30cm³ and for EDH with extenuating factors (GCS less than 9, clot thickness greater than 15mm, midline shift greater than 5mm or focal neurological deficits) [245]. Patients should be considered for the evacuation of subdural hematomas (SDH) that are larger than 1 cm or associated with midline shift greater than 5 mm, a rapidly declining GCS, GCS less than 9, asymmetric or fixed and dilated pupils, or intracranial pressure (ICP) > 20 mmHg [246]. A randomized controlled trial of early surgical evacuation in patients with traumatic intracranial hemorrhage (ICH) greater than 10mL, 2/3 of whom had GCS between 9 and 14, found improved 6-month mortality in the surgical group. Effects on delirium were not reported [247].

6.3.2. Intracranial Pressure Management

6.3.2.1. Monitoring

Patients with severe TBI (indicated by a Glasgow Coma Score of 8 or less and abnormalities on CT scan) should be considered for intracranial pressure monitoring once the patient's airway and hemodynamic stability have been addressed. This may be accomplished using intraparenchymal monitors (placed directly into brain tissue) or by placement of an extraventricular drain (EVD) connected to an external pressure transducer or fiber optic catheter, allowing for therapeutic ventricular drainage while performing continuous intracranial pressure monitoring [248]. The EVD and fiber optic cable have the benefit of providing a method of lowering ICP by continuous or intermittent CSF drainage. The target ICP is less than or equal to 20 mmHg, with a corresponding cerebral perfusion pressure (estimated as the difference between mean arterial pressure and ICP) of 50-70 mmHg.

In a retrospective matched cohort study of patients in the Brain Trauma Research Center (BTRC) database, continuous drainage was associated with, on average 5.7 mmHg lower pressures and significantly lower burden of intracranial hypertension (ICP > 20 mmHg) than intermittent drainage [249]. The continuous drainage approach may increase risk for complications such as catheter clotting, ventriculitis, CSF leak or hemorrhage [250]. Currently, the intraventricular ICP

catheter is considered the most accurate method of ICP monitoring. This design eliminates the need for a fluid-filled system to communicate pressure to an external transducer, thereby significantly reducing the risk of these complications [248]. Nowadays, the intraventricular ICP catheter is the most accurate monitoring method. This design eliminates the need for a fluid-filled system to communicate pressure to an external transducer, thereby significantly reducing the risk of these complications [185].

6.3.2.2. Hypertonic Saline and Mannitol

Hypertonic saline and mannitol are the most commonly used agents for the pharmacologic treatment of increased intracranial pressure. Intravascular hyperosmolarity creates an osmolar gradient for water egress from brain parenchyma to the intravascular space, thereby reducing brain volume [251]. In the case of mannitol, there is also a decrease in blood viscosity and constriction of cerebral conductance vessels, contributing to the reduction of intracerebral blood volume and intracranial pressure [252]. Based on limited data, there is weak evidence to suggest that hypertonic saline is no better than mannitol in efficacy and safety in the long-term management of acute traumatic brain injury [253]. Since vasogenic edema sustained by inflammation may prove to be refractory to hyperosmolar therapy, and the principle of only 11% of edema fluid shunted into the blood vessels [33, 66] has to be taken under consideration, therapeutic inhibition of inflammation [254-257] and thus of vasogenic edema offers promising perspectives when anti-inflammatory agents are available for clinical studies.

6.3.2.3. Barbiturate Coma

Patients with refractory intracranial hypertension in the absence of mass lesions appropriate for surgical intervention can be considered for barbiturate therapy. Pentobarbital suppresses glutamate excitation and prolongs GABA inhibition at the postsynaptic membranes, resulting in a widespread decrease in neuronal activity [258-260]. Treatment with continuous pentobarbital infusion under continuous EEG monitoring can effectively reduce cerebral perfusion pressure, and in one study resulted in 40% hospital survival rate and 68% rate of good functional outcomes at 1 year after injury [261]. These benefits must be weighed against the risks to the patient, such as systemic hypotension, hypo- or hyperkalemia and feeding intolerance [185, 262]. Hemodynamic stability is essential before and during barbiturate therapy [185]. Alternative sedative regimens include propofol with morphine or benzodiazepines, although the latter has been associated with an increased risk of delirium [263]. These sedatives may also decrease systemic blood pressure, resulting in reductions in cerebral perfusion pressure, and for this reason ketamine has been proposed as an attractive alternative for maintenance of pharmacologic coma [264]. Dexmedetomidine has also gained some popularity in the management of refractory intracranial hypertension and shows some promise as an adjunct therapy [265], although evidence for its routine use in this context is yet to be established.

6.3.2.4. Decompression

A randomized clinical trial of bilateral frontotemporo-parietal decompressive craniectomy in 155 adult patients with

diffuse TBI and refractory ICH (the DECRA Trial) demonstrated lower ICP and shorter ICU lengths of stay with this intervention, however, these results were tempered by diminished long term functional outcomes and lack of improvement in mortality at 6 months after injury [266]. A second randomized trial in 408 adult and pediatric patients with TBI and refractory ICP (the RESCUEicp Trial) demonstrated lower mortality and disability rates at 6 months after injury, but higher rates of vegetative state [267]. The effects of this intervention on delirium associated with TBI have not been directly evaluated.

6.3.2.5. Hypothermia

An early systematic review of randomized controlled trials evaluating therapeutic hypothermia in TBI found improved mortality and neurologic function with this intervention [268]. However, two more recent reviews challenged these findings, raising concerns of risk of bias and quality of evidence [269, 270]. The multicenter Prophylactic Hypothermia Trial to Lessen Traumatic Brain Injury-Randomized Controlled Trial (POLAR-RCT) compared 266 patients on prophylactic hypothermia to 245 patients with normothermic management and found substantially similar 6-month neurologic and functional outcomes in the two groups [271].

6.3.3. Seizure Management

In patients with serious head trauma, seizure prophylaxis with phenytoin (a voltage-dependent sodium channel antagonist [272]) or levetiracetam (an N-type calcium channel inhibitor that exerts its effects through modulation of the synaptic vesicle-2A protein [273, 274]) decreases the risk of early posttraumatic seizures and is recommended during the first 7 days [275, 276]. Given that nonconvulsive seizures commonly present with signs of delirium such as confusion, inattention and fluctuations in mental status, a low threshold should be maintained for considering EEG monitoring in patients with TBI and delirium. The Brain Trauma Foundation and the Guidelines for the Management of Severe Traumatic Brain Injury, Fourth Edition [185] do not suggest routine continuous EEG monitoring in TBI patients, focusing instead on ICP, CPP and blood pressure management [185]. Nonetheless, seizures are frequently associated with TBI. Posttraumatic seizures occur in 21–27% of moderate to severe TBI patients and are generally associated with haemorrhagic lesions of the temporal lobe [277–279]. The first event of recorded seizures typically occurs during the first 24 hours after TBI, with over one-third being nonconvulsive in nature [277]. TBI-related seizures can also be induced by increased ICP, cerebral metabolic crisis associated with disturbances in oxidative metabolism and glucose consumption, and impaired redox state of the brain [279]. A prospective cohort study of continuous EEG in 50 inpatients greater than 65 years of age with delirium found 12% in non-convulsive status epilepticus. Thirty percent of participants had epileptiform activity on EEG, suggesting the delirium was caused by intermittent seizures [280]. In a retrospective cohort of older adults with delirium who received EEG in the emergency room, epileptiform activity was found in 15% [281]. Seizures may be a significant risk factor for post-TBI delirium. Continuous electroencephalography may improve the detection of seizures, particularly those that are non-convulsive in

nature, and should be considered among the guidelines for the management of traumatic brain injury.

Convulsive or nonconvulsive seizures that are refractory to standard prophylactic doses of antiepileptic medications should prompt consideration of dose escalation and neurological consultation. The first-line therapy for status epilepticus in this context is a fast-acting benzodiazepine such as lorazepam or midazolam, to be given intravenously. Accepted second-line therapies include intravenous phenytoin, fosphenytoin (a phenytoin pro-drug with lower risk of cardiac and subcutaneous adverse effects [282]), valproate [283] or levetiracetam [284, 285]. Pharmacologic coma, *e.g.* with propofol, barbiturates or ketamine, is an accepted therapy for refractory status epilepticus [286]. Ketamine is novel among the drugs typically used to control seizures due to its use-dependent blockade of excitatory synaptic activity via modulation of the N-methyl-D-aspartate (NMDA) receptor [287].

Status epilepticus that persists or recurs despite anesthetic coma is termed “super-refractory” [286]. A number of novel neurotherapies have been investigated for this clinical scenario. For example, allopregnanolone, a positive modulator of synaptic and extrasynaptic GABA type A receptors, showed success in small case series [288, 289], but a phase III clinical trial of brexanolone (a proprietary formulation of the same drug) in 132 patients at 122 sites around the world failed to show a benefit over placebo infusion [290].

6.3.4. Management of Post-Intensive Care Syndrome

All critical care survivors are at risk for Post Intensive Care Syndrome (PICS), a potentially crippling combination of physical, psychological and cognitive sequelae of critical illness and ICU care [291–293]. The psychological impacts of PICS can affect family members and caregivers of critically ill patients as well [294]. Delirium in the ICU increases risk for PICS [295], and TBI patients and their families may be at even higher risk because of the neurologic compromise intrinsic to their injury [296]. Patients and their families should be evaluated for PICS and those having signs and symptoms of this disorder should be managed by a multidisciplinary team including intensivists, neuropsychiatrists, respiratory and physical therapists, and with the consideration of pharmacological and non-pharmacological interventions as appropriate [219, 297].

7. FUTURE DIRECTIONS

Further investigation of the unique problems, pathophysiology and pharmacologic needs of ICU delirium in TBI is desperately needed to reduce the burden of disease in patients with moderate to severe TBI. This will depend on elucidation of the neuropathological and neurophysiological characteristics of each etiologic contributor independently and when they occur in concert, and on further elucidation of the mechanistic pathways by which these contributors lead to delirium in TBI patients. It will also require a detailed epidemiologic and clinical understanding of the presentations of delirium in TBI patients, and further evaluation of the efficacy of delirium interventions in this population.

A significant decrease in TBI-induced biochemical injury seems to be a promising option for delirium prevention or

treatment. Hence, further systematic clinical study should be performed to confirm the experimentally documented neuroprotective and neuroregenerative effects of individual medications and medication classes, especially flavonoids as described above, in treatment and prevention of delirium in TBI patients, and of the effects of these medications on long term recovery and cognition.

CONCLUSION

Delirium in patients admitted to the ICU after traumatic brain injury is very common, occurring in 50-75% of patients. The changes persist in up to 70% of patients with TBI who suffer from delirium upon arrival to inpatient neurorehabilitation.

Delirium is a devastating form of brain dysfunction linked to increased mortality, prolonged hospital stay, increased financial cost and long-term cognitive impairment in the TBI population. Therefore, all ICU patients must be actively monitored for the presence of delirium during their entire hospital stay.

The etiology of delirium is not fully elucidated but known to be multifactorial. Both focal or diffuse brain dysfunction due to the primary injury as well as secondary brain injuries such as due to increased intracranial pressure (ICP) from hemorrhage or edematous states multiple subjects in TBI patients. However, other etiologies occurring in all ICU patients are also common, including adverse effects of intravenous sedatives or other centrally acting drugs, organ failure leading to metabolic disequilibrium or systemic inflammatory response secondary to sepsis. The mechanisms by which these pathways induce or exacerbate delirium are the subject of ongoing inquiry.

Optimal treatment of delirium associated with traumatic brain injury is determined by the etiology. Attention must be paid to adequate pain control, avoidance of oversedation and providing early mobility adequate to patient functional status after TBI. For decades, nonpharmacologic interventions have been the cornerstone of delirium management and treatment. Family involvement and active engagement cannot be over-emphasized. To prevent delirium in TBI patients, attention to the ICU environment must be paid to prevent sleep and sensory deprivation, reduce overstimulation and psychological stress.

LIST OF ABBREVIATIONS

AA	=	Arachidonic acid
BBB	=	Blood-brain barrier
CNS	=	Central nervous system
COI	=	Cavity of injury
CPP	=	Cerebral perfusion pressure
CT	=	Computed tomography
ECoG	=	Electrocorticography
EEG	=	Electroencephalography
EVD	=	Extraventricular drain
GABA	=	Gamma-aminobutyric acid

HAS	=	Haute Autorité de Santé
HT	=	Hydroxytryptamine
ICDSC	=	Intensive Care Delirium Screening Checklist
ICH	=	Intracranial hemorrhage
ICP	=	Intracranial pressure
ICU	=	Intensive care unit
IL	=	Interleukin
INCOG	=	International Panel on Cognition
INF	=	Interferon
MCP	=	Monocyte chemoattractant protein
MRI	=	Magnetic resonance imaging
NMDA	=	N-methyl-D-aspartate
NSAID	=	Non-steroidal anti-inflammatory drug
PICS	=	Post-Intensive Care Syndrome
RASS	=	Richmond agitation-sedation scale
SAT	=	Spontaneous awakening trial
SBT	=	Spontaneous breathing trial
SCCM	=	Society for Critical Care Medicine
SCI	=	Spinal cord injury
SOFMER	=	Société Française de Médecine physique et Réadaptation
TBI	=	Traumatic brain injury
TGF	=	Transforming growth factor
TNF	=	Tumor necrosis factor

CONSENT FOR PUBLICATION

Not applicable.

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CONFLICT OF INTEREST

Dr. Williams Roberson declares no conflicts of interest. Drs. Patel and Ely are supported by the National Institutes of Health (NIH R01 AG058639, R01 GM120484, and I01 RX002992) and declare no conflicts of interest. Dr. Dabrowski, Dr. Pakulski and Dr. Kotfis declare no conflicts of interest.

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