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Metabolic Encephalopathies and Delirium

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Introduction

The term encephalopathy derives from the Greek encephalos (brain) and pathos (suffering or experience). Kinnier Wilson was the first to coin the term metabolic encephalopathy to describe the clinical presentation of a global cerebral dysfunction induced by systemic factors. This is a common encounter in hospitals and especially Intensive Care Units (ICU), where it can begin as a subtle cognitive change, usually missed initially, progress to a readily detectable delirium, and eventually resolve or lead to coma and death. The words “encephalopathy” and “delirium” are often used interchangeably.

Delirium is encountered frequently in hospitalized patients. The incidence of delirium has been estimated at up to 22% of medical patients, 11–35% of surgical patients and 80% of ICU patients [1,2]. Older patients are particularly prone to developing delirium when hospitalized, with up to 50% incidence [3-5]. The estimated cost burden to the US in 2004 was between $4 and 16 billion [6].

Many etiologies of acute encephalopathy can be easily detected with neuroimaging, as an underlying structural etiology that can be well visualized. A frequent reason for a neurological consultation, however, remains non-structural causes of altered mental status and their management considerations. This will be the focus of this chapter.

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1. Pathophysiology

The various etiologies of metabolic encephalopathy are presented in Table 1. In general, they could be divided into drug intoxication/withdrawal, electrolyte and glucose abnormalities, major organ dysfunction, nutritional deficiencies, exposure to extraneous toxins, paraneoplastic syndromes and sleep or sensory deprivation. Non-metabolic causes of delirium include focal cerebral lesions, infectious processes and epileptic phenomena. Strokes and other lesions that involve the temporal lobes, fusiform and lingual gyri, caudate nucleus, and anterior cingulum have been reported to cause an acute hyperactive delirium [7]. Non-convulsive seizures or status epilepticus have also been described as a cause, both requiring continuous electroencephalography to be detected [8] [9-13]. These non-systemic conditions fulfilling delirium criteria have been called “delirium symptoms” by some experts, arguing that they may not represent true delirium [14].

Table 1:
Etiologies of Metabolic Encephalopathy

Medications	Anticholinergic drugs, antihistamines, tricyclic antidepressants, narcotic analgesics (especially meperidine), antimicrobials (including cefepime and metronidazole), benzodiazepines, barbiturates, anesthetics, digoxin, corticosteroids, propranolol, lithium, theophylline, histamine-2 receptor antagonists, proton-pump inhibitors, antiparkinsonian agents, antiepileptic drugs, immunosuppressant agents (tacrolimus, cyclosporine, ifosfamide), antineoplastic agents, recreational drugs (abuse or withdrawal), herbal preparations
Toxins	Metals (arsenic, lead, mercury), ethylene glycol, methanol, cyanide, carbon monoxide (CO)
Metabolic	Liver failure, uremia, hypoglycemia, hyperglycemia, electrolyte abnormalities, hypercarbia, hypoxia
Endocrine	Thyroid, parathyroid, pituitary, adrenal gland dysfunction, uncontrolled diabetes, pancreatitis
Infectious	Meningitis, encephalitis, abscess, bacteremia, sepsis
Neoplastic	Systemic cancer, paraneoplastic syndromes, CNS tumors, carcinomatous meningitis
Nutritional	Thiamine, B12, niacin, folic acid deficiencies
Miscellaneous	Severe anemia, dehydration, volume overload, burns, fat embolism, chronic obstructive pulmonary disease (COPD), migraine, posterior reversible leukoencephalopathy syndrome (PRES), sensory deprivation, sleep deprivation, Reye syndrome, idiopathic recurrent stupor (endozepine stupor)

**Modified from [15]*

Risk factors that have been associated with delirium in hospitalized, critically ill patients include [15-17]:

- Age > 70 years
- Male gender
- Poor functional status
- Malnutrition
- Substance abuse
- Hypertension
- Emergency surgery
- Polytrauma
- Metabolic acidosis
- Mechanical ventilation
- Organ failure
- Pre-morbid medical conditions or cognitive impairment (dementia)
- Polypharmacy, including centrally acting medications
- Physical restraints
- Visual or hearing impairment
- Prior history of delirium
- Lack of sunlight or visitors
- Sleep deprivation
- Number of catheters and drains in patients with blood stream infections

A prediction model for the development of ICU delirium, the PRE-DELIRIC score, uses 10 risk factors and performs better than provider predictions [18] .

2. Clinical Presentation

Despite the protean symptomatology of delirium, specific diagnostic criteria have been developed (Table 2). Standardized delirium detection scales have also been used but are nonspecific as all etiologies could present with similar signs and symptoms. These include the Confusion Assessment Method for the Intensive Care Unit (CAM-ICU) [19] and the Intensive Care Delirium Screening Checklist (ICDSC) [20].

Table 2:
DSM-V Diagnostic Criteria for Delirium Due to a General Medical Condition[21]

A.	Disturbance in *attention* (i.e., reduced ability to direct, focus, sustain, and shift attention) and awareness (reduced *orientation to the environment*).
B.	The disturbance develops over a short period of time (usually hours to a few days), *represents an acute change from baseline attention and awareness*, and tends to fluctuate in severity during the course of a day
C.	An additional disturbance in cognition (e.g. memory deficit, disorientation, language, visuospatial ability, or perception).
D.	*The disturbances in Criteria A and C* are not better explained by a pre-existing, established or evolving neurocognitive disorder and *do not occur in the context of a severely reduced level of arousal such as coma.*
E.	There is evidence from the history, physical examination or laboratory findings that the disturbance is *a direct* physiological consequence of another medical condition, *substance intoxication or withdrawal (i.e. due to a drug of abuse or to a medication), or exposure to a toxin, or is due to multiple etiologies*.

Three types of delirium have been described in the ICU based on the motor activity of the patient: hyperactive (1.6%), hypoactive (43.5%) and mixed (54.1%). Hyperactive delirium carries a better prognosis and often presents as hallucinations in younger patients. By contrast, hypoactive delirium is frequently characterized as apathy in older patients and is associated with a worse prognosis[23].

In the majority of cases of metabolic encephalopathy, the patient has a non-focal exam with alterations in vital signs such as tachycardia, hypo- or hypertension, tachypnea, or fever. A detailed systematic exam, however, may reveal clues. For example, fever and nuchal rigidity for meningitis, clammy pale extremities with hypotension in shock, jaundice in hepatic encephalopathy, fruity breath from acetone expiration in diabetic ketoacidosis, blue gums with lead, Mees' lines with arsenic and acrodynia with mercury intoxications [22]. Although less common, metabolic derangements can occasionally present with focality, such as focal-onset seizure with hypoglycemia or asymmetric ophthalmoplegia and ataxia with thiamine deficiency.

Although there is no specific biomarker for delirium, a basic or extended laboratory workup may reveal its cause (Table 3 and Fig 1). Many drug levels not routinely used in clinical practice can only be measured in specialized laboratories. Additional serum should be stored when possible in case the causative agent is not initially identified.

Table 3:
Laboratory Investigation for Metabolic Encephalopathies

1.	Complete blood count with differential, ESR and CRP
2.	Serum electrolytes, BUN, creatinine, glucose.
3.	Thyroid, parathyroid and adrenal hormone evaluation
4.	Liver function tests, amylase, lipase, ammonia
5.	Troponin levels
6.	HIV ELISA after patient's consent (if required)
7.	Arterial blood gases with lactate level
8.	Cerebrospinal fluid evaluation, including cytology.
9.	Body fluid cultures (blood, urine, stool, sputum, CSF)
10.	Culture from/of indwelling catheters
11.	Serum and urine toxicology, including antiepileptic drug levels or heavy metals

Modified from [15]

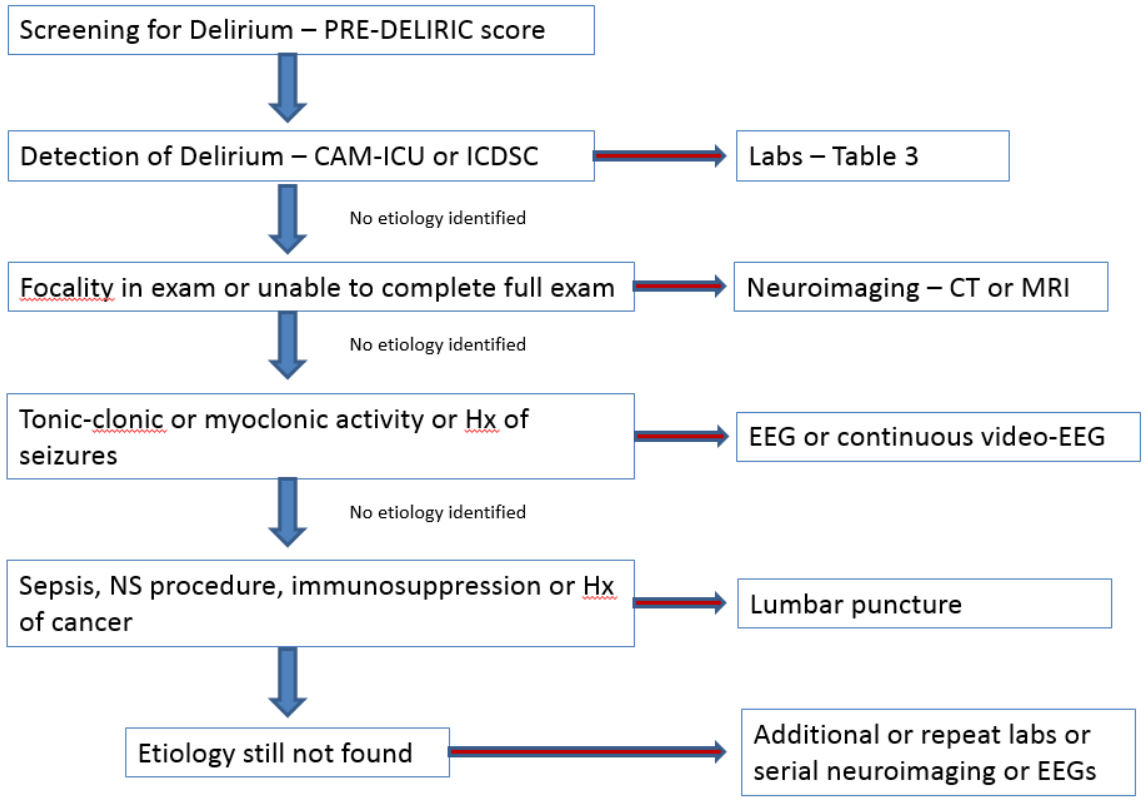


Figure 1: Diagnostic Flowsheet

EEG may show generalized slowing of the background or triphasic waves which usually occur with hepatic or uremic encephalopathy but are not specific. As mentioned above, it could also detect non-convulsive seizures or status as a modifiable cause. Neuroimaging studies can help to exclude structural lesions and allow a safer lumbar puncture, as well as occasionally narrow the potential etiologies of toxic-metabolic encephalopathies. MRI may reveal specific findings in conditions such as osmotic demyelination, carbon monoxide poisoning, methanol,

ethylene glycol, cyclosporine or metronidazole toxicity. Lumbar puncture may be less useful in hospital-acquired delirium to exclude meningitis than in patients who developed it during pre-hospitalization [23]. However, one should consider it in post-procedure neurosurgical, immunosuppressed or post-traumatic brain injury patients. It should only be performed after neuroimaging in patients with focality in the neurological exam or in stuporous or comatose patients.

3. Treatment and Prevention of Acute Metabolic Encephalopathies

Preventative, non-pharmacologic interventions to avoid escalation of delirium symptoms are of utmost importance. A bundled approach, including patient reorientation, noise reduction, avoidance of unnecessary procedures, decrease of restraint use, early mobilization, promotion of sleep or exposure to daylight and limiting sensory deprivation (glasses, hearing aids) has been shown to be effective. Efficacy has mainly been demonstrated in non-ICU patients, since it is unclear how well these measures can be implemented in an ICU [23-25]. In a recent metanalysis, however, integration of these multicomponent strategies with PAD (pain, agitation, delirium) [26] or the ABCED bundle (Assess, Prevent, and Manage Pain; Both Spontaneous Awakening Trials and spontaneous Breathing Trials; Choice of Analgesia and Sedation; Delirium: Assess, Prevent, and Manage; Early Mobility and Exercise) [27] led to decreased ICU length of stay and mortality [28].

A variety of antipsychotics and sedatives have been utilized to control symptoms of various encephalopathies and in the management of delirium (Table 4). There is little evidence to support superiority of one agent over another, and choice of agent is frequently based on individual patient response and risk of adverse effects[31].

Table 4:
Characteristics of Selected Antipsychotics Frequently Used in the Management of Encephalopathies and Delirium

Agent	Receptor	EPS	QTc	NMS	Clinical Pearls
Haloperidol	DA2 (DA1)	+++	++	+++	• IV administration has been associated with QT prolongation. ECG monitoring is recommended. • EPS more common with oral administration than IV. • Tardive dyskinesia is associated with long term exposure. • Available dosage forms: IV, IM, PO
Olanzapine	DA, 5-HT, alpha-1, HA1, MI	0/+	+	0/+	• Generally well tolerated. Common adverse effects include sedation and hypotension. • Available dosage forms: IM, PO, ODT
Risperidone	DA, 5-HT, alpha 1, alpha-2, HA2	+/++	+/++	+	• Risk for EPS increases with higher doses (≥6 mg/day). • Common adverse effect include sedation, orthostatic hypotension, and hyperprolactinemia • Available dosage forms: IM, PO, ODT
Ziprasidone	DA, 5HT, alpha 1	0/+	++	0/+	• Use caution if combining with other agents that prolong QTc. • Administering with food increases exposure. • Available dosage forms: IM, PO
Aripiprazole	DA, 5HT, alpha 1, HA1	0/+	+	+	• Generally well tolerated. Common adverse effects include headache, anxiety, insomnia, somnolence, constipation. • Available dosage forms: IM, PO, ODT
Quetiapine	DA, 5HT, alpha 1, HA1, M1	0/+	+/++	+	• Higher incidence of sedation compared to other antipyschotics. • Available dosage forms: PO

ECG: echocardiogram; EPS: extra pyramidal symptoms; QTc: QTc interval prolongation; NMS: neuroleptic malignant syndrome; IV: intravenous; IM: intramuscular; PO: oral; ODT: oral disintegrating tablet
0 = none + = low ++ = moderate +++ = high

4. Selected Metabolic Encephalopathies

4.1. Sepsis-Associated Encephalopathy

Sepsis-associated encephalopathy **(**SAE) has been reported in 9-71% of patients with sepsis and may increase mortality and morbidity. SAE is clinically similar to other encephalopathies, with signs and symptoms of agitation, asterixis, tremor, paratonic rigidity, multifocal myoclonus and even coma. Long-term consequences of SAE have been described [29]. New moderate to severe cognitive impairment three years after recovery has been reported in 17% of patients [30]. Diffuse cognitive deficits, atrophy in the left hippocampus and diffuse slow wave frequencies on EEG have also been reported 6-24 months after surviving sepsis [31]. Developing dementia within three years after admission to an ICU for infection or severe sepsis or acute neurologic dysfunction has also been reported [32].

The pathophysiology of SAE is very complex. Systemic inflammation causes activation of the vagus nerve and circumventricular organs which leads to brainstem and hypothalamic activation (nucleus tractus solitarius, paraventricular nuclei). Both signal behavioral, neuroendocrine or neurovegetative alterations, which may modulate neurosecretion and neurotransmission (especially enhanced dopaminergic and reduced GABA-ergic and cholinergic activity) [33]. Additionally, lipopolysaccharides and proinflammatory cytokines activate the brain vessel endothelium, which leads to altered vascular microcirculation and breakdown of the BBB. Neurotoxic factors then pass into the brain parenchyma, affecting autoregulation of cerebral blood flow, inducing macro-ischemias/hemorrhages, and at a cellular level enhancing microglial activation and nitric oxide generation. This ultimately results in oxidative stress and promotion of mitochondrial dysfunction and cellular apoptosis [29,33-35].

EEG can help differentiate between SAE and non-convulsive seizures. In a recent study of MICU patients with sepsis, non-convulsive seizures or periodic discharges were found in 11% and in 25% of cases, respectively [36]. In another study using Transcranial Doppler, pulsatility index > 1.3 in the middle cerebral artery on the first day of sepsis could predict a positive CAM-ICU test with 95% sensitivity and 88% specificity, and was an independent predictor of delirium [37].

No specific treatments for SAE, other than treating the systemic illness, are available [38].

4.2 Hepatic Encephalopathy

Hepatic encephalopathy (HE) has been associated with acute, progressive, or chronic liver failure. Cerebral edema, the most fearsome neurologic complication, is both cytotoxic and vasogenic. The former is related to astrocytic swelling because of neurotoxin accumulation (ammonia, short-medium chain fatty acids, phenols, mercaptans), false neurotransmitters, activation of GABA receptors by endogenous benzodiazepines (endozepines) and decrease production of glutamate This leads to decreased excitatory transmission and excessive neuroinhibition [39]. The latter is related to alterations in BBB permeability, increased cerebral blood flow and systemic inflammation.

A clinical grading system has been developed (Table 5). The transition from grade 1 to 4 may be more gradual with chronic liver failure than with acute [40]. Diagnosis is supported by elevated serum ammonia, neuroimaging showing diffuse edema and occasionally hyperintense signal in the globus pallidus, subthalamic area and midbrain on T1-weighed MRI sequence, and triphasic waves on the EEG. MR spectroscopy can be used to detect decreased choline and myoinositol and increased glutamine and glutamate, but the clinical application of these findings is questionable [41].

Table 5: West Haven Grading of Hepatic Encephalopathy[42]

Grade 1	Trivial lack of awareness Euphoria or anxiety Shortened attention span Impaired performance on addition
Grade 2	Lethargy or apathy Minimal disorientation for time or place Subtle personality change Inappropriate behavior Impaired performance of subtraction
Grade 3	Somnolence to semi-stupor, but responsive to verbal stimuli Confusion Gross disorientation
Grade 4	Coma

Treatment with specific pharmacologic agents is a mainstay of the management of overt hepatic encephalopathy (OHE) and its secondary prevention. Lactulose, a non-absorbable disaccharide, is considered first line for the treatment of OHE despite controversial evidence supporting its use. Lactulose administrations are titrated based on stool output, typically started at 20-30 grams orally two to four times daily and should not be adjusted based on serum ammonia levels. Inadequate response to lactulose should prompt further investigation into alternative causes of symptomatology. Rifaximin has been utilized as an effective add-on therapy to lactulose for secondary prophylaxis at a dose of 550 mg orally twice daily; however, its role in the treatment of OHE is unclear. Neomycin and metronidazole have also been investigated as treatment options for OHE and may be used short term as alternatives to lactulose[43]. In case of extreme hyperammonemia or no response to pharmacological interventions, renal replacement therapy to dialyze the ammonia out, may also be considered.

Additional therapeutic measures to manage cerebral edema in liver failure patients include intracranial pressure (ICP) monitoring and management with placement of ICP monitors, sedation with low-dose propofol, osmotic therapy [44], normothermia or mild hypothermia [45], slow renal replacement therapy if hepatorenal syndrome occurs (usually continuous venovenous hemofiltration or sustained low-efficiency dialysis to avoid rapid osmotic shifts) and lastly, orthotopic liver transplantation. Placement of ICP monitors has been recently questioned. More than half of 629 patients with acute liver failure and grade III/IV HE were found to have elevated ICP in a retrospective study. Despite the fact that hemorrhagic complications from monitor placement were seen in only 7% of patients, ICP monitoring did not confer a significant 21-day mortality benefit in those with acetaminophen toxicity, whereas in patients with non-acetaminophen acute liver failure, it might have been associated with worse outcomes [46].

4.3 Uremic Encephalopathy

Uremic encephalopathy (UE) is usually more severe after acute renal failure (ARF) but can be witnessed with chronic renal failure. Because ARF often complicates sepsis, it may difficult to differentiate UE from SAE. Accumulation of dialyzable uremic toxins (urea, guanidine compounds, hippuric acid, polyamines, phenols, indolic acids, myoinositol) have been implicated in the pathogenesis, in addition to sodium-potassium-ATPase dysfunction and increased parathyroid hormone with elevation of intracellular sodium and calcium, respectively. Guanidine compounds have been shown to antagonize GABAergic receptors and activate NMDA receptors, leading to enhanced cortical excitability. A distinct dialysis disequilibrium syndrome may also occur in patients with high pre-dialysis urea and metabolic acidosis who undergo rapid hemodialysis resulting in fast osmolar shifts and development of brain edema. This may be due to development of an osmolar gradient favoring water influx to the brain after rapid peripheral urea decreases or to an increased production of idiogenic intracellular osmoles.

Clinically, the syndrome starts with subtle mental and emotional changes and can progress to full blown delirium, seizures and coma. Motor phenomena, such as action tremor, asterixis, hypereflexia, myoclonus, anorexia and, in longstanding cases, peripheral neuropathy can also be part of the clinical evolution. Neuroimaging may reveal diffuse cerebral atrophy or multifocal relatively symmetric, gyriform high signal intensity on T2WI/FLAIR images and low signal intensity on T1WI in the bilateral frontal and parieto-occipital lobes [47]. The lentiform “fork sign” is a characteristic MRI FLAIR-sequence finding in patients with fluctuating, reversible parkinsonism and UE [48], which may be associated with metabolic acidosis [49]. The EEG in patients with UE shows generalized slowing with triphasic waves, paroxysmal frontally-predominant high voltage delta waves and occasionally paradoxical accentuation of the background rhythm with eye opening [40].

Therapeutic measures include renal replacement therapy and renal transplantation. Signs and symptoms typically begin to reverse within days or weeks. Correction of anemia and thiamine deficiency may also lead to cognitive improvement [40,50].

4.4 Pulmonary Encephalopathy and Carbon Monoxide Poisoning

Frequently seen in patients with chronic respiratory insufficiency, pulmonary encephalopathy can also occur in other conditions where neuro-respiratory control of gas exchange is impaired. Brainstem lesions affecting the respiratory center, such as stroke, hemorrhage or compression, upper spinal cord injuries, polyneuropathies, such as Guillain-Barre syndrome or critical illness polyneuropathy, neuromuscular junction blockade, such in myasthenia gravis or Lambert-Eaton syndrome, myopathies affecting the diaphragm or intercostal muscles, are characteristic examples.

The pathophysiological basis is hypoxia and/or hypercapnia. As oxygen availability to the brain is decreased or CO_2 is increased, cerebral vasodilation ensues and cerebral blood flow increases with ICP elevation. Carbon monoxide (CO) also affects the respiratory chain by binding to cytochrome c oxidase, worsening tissue hypoxia and creating deleterious reactive O_2 species [51].

Additionally, CO poisoning may have a biphasic course. Initially symptoms of confusion, difficulty concentrating, dizziness, nausea, headache may present with 20-30% carboxy-hemoglobin (CO Hg) concentrations. Higher levels of CO Hg lead to ataxia, hallucinations, stupor and coma, with death usually occurring at levels of 80% or higher. Among survivors, 10-30% may develop extrapyramidal symptoms, memory loss, incontinence and psychotic behavior 3-240 days later. MRI in these delayed cases shows symmetrical bilateral pallidal, entire basal ganglia hyperintensities or symmetrical bilateral white matter changes in T2 with decreased ADC values [40,41].

Although the clinical presentation of pulmonary encephalopathy may not differ from other types of delirium, occasionally papilledema is present in more chronic cases. Also a milder, indolent form, mainly with cognitive impairment only proven by neuropsychologic battery tests, may be present (as in sleep apnea patients).

Treatment is administration of oxygen to correct hypoxia, hyperbaric oxygen to enhance the elimination of CO Hg (from 4-5 hours to 20 minutes at 3 atmospheres; this treatment is still considered controversial) or invasive/non-invasive ventilation to improve the hypercarbia [52].

4.5 Posterior Reversible Leukoencephalopathy Syndrome

PRES was initially recognized in cases of eclampsia, severe hypertension and with immunosuppressive agents after transplantation. However, many other conditions have been associated, including sepsis, SIRS, renal or multi-organ failure, post-transplantation, autoimmune diseases (e.g., systemic lupus, scleroderma, granulomatosis with angiitis (formerly “Wegener’s Syndrome”), polyarteritis nodosa, porphyria), electrolyte derangements (hypomagnesemia, hypercalcemia), hypocholesterolemia, CSF leak (cerebral hypotension syndrome) or hyperperfusion syndrome post-CEA or during hypertensive treatment for post-SAH vasospasm [40]. A growing number of medications including immunosuppressant drugs, chemotherapeutic or anti-angiogenic agents have been associated with the development of PRES (Table 5).

Table 6:
Causative Agents Incited in PRES

Immunosuppressive agents	Anti-CD20 inhibitors (rituximab) Calcineurin inhibitors (tacrolimus) CTLA inhibitors (ipilumumab) EGFR inhibitors (cetuximab) IL-2 inhibitors (cyclosporine) mTOR kinase inhibitors (everolimus, sirolimus) PD-1 inhibitors (pembrolizumab) Proteasome inhibitors (bortezomib) Purine synthesis inhibitors (azathioprine) TNF inhibitors (infliximab, adulimumab) TK inhibitors (pazopanib, sorafenib, sunitinib) VEGR inhibitors (bevacizumab, cedrane, regorafenib)
Chemotherapeutic agents	Asparagine inhibitors (L-asparginase) DNA synthesis inhibitors (cytarabine) Methotrexate Paclitaxel Platinum based chemotherapy (cisplatin, oxaliplatin, carboplatin) Pyrimidine antimetabolites (gemcitabine) Vincristine
Other medications	Carbamazepine Interferon alpha Intravenous immune globulin (IVIG) Linezolid Lithium Methyprednisolone Sphingosin 1-phosphate receptor agonists (fingolimod)

Clinically PRES presents with headache, amaurosis/hemianopsia, confusion, lethargy or coma and nausea/vomiting, in descending frequency. Up to 90% of cases present with seizures. Tinnitus and vertigo are also frequently reported [53]. Hypertension is found in 50-70% of cases. The lesions detected on MRI are generally parieto-occipital, but can also be more anterior in the frontal lobes [54] or affect watershed or subcortical areas. Although the pathophysiology is controversial, the presence of vasogenic and occasionally cytotoxic edema has been explained by two opposing theories: hypertension with defective autoregulation (beyond the upper inflexion point of the curve) and hyperperfusion, or endothelial injury [55] associated with vasoconstriction and leading to hypoperfusion [56]. Additional theories include the immunogenic theory with T-cell activation and cytokine release, leading to increased endothelial cell permeability and the neuropeptide theory, whereas release of potent vasoconstrictors (endothelin-1, prostacyclin and thromboxane A2 lead to vasospasm and cerebral ischemia [53].

The mainstay of treatment includes blood pressure regulation, discontinuing offending agents and treating any predisposing underlying condition. In up to 25% of patients, the lesions are irreversible and the deficits persistent [40]. Up to 44% with severe PRES have severe functional impairments by day 90. Hyperglycemia on day 1 and time to causative-factor control are strong early predictors of outcomes [57].

4.6 Alcohol Withdrawal Encephalopathy

Also known as delirium tremens in its most severe form, alcohol withdrawal encephalopathy can occur in 5-40% of patients admitted with alcohol dependence and carries a 15% mortality rate if left untreated. Hyperactivity and tremulousness start within few hours after alcohol cessation and peak at 10-30 hours. Seizures, either generalized or focal, may follow with a typical onset of 6-48 hours and peak at 13-24 hours. Auditory, visual or tactile hallucinations may also occur at this time and with a typical duration of 1-6 days. Delirium tremens with severe autonomic hyperactivity may also occur with a typical onset of 60-96 hours [58].

Key treatment measures include fluid and electrolyte replacement, thiamine supplementation, and benzodiazepine administration. Symptom-triggered administration of benzodiazepines has generally been associated with similar clinical outcomes and decreased hospital lengths of stay compared to fixed dose approaches. For resistant cases, propofol, dexmedetomidine or barbiturate administration can be considered. Because intracranial hemorrhage is also prevalent with alcoholism, neuroimaging should be obtained for new-onset seizures if the neurological exam confirms focality or if overt trauma is present.

4.7 Wernicke's Encephalopathy

Wernicke's encephalopathy can result from alcoholism, malnutrition, cancer, chemotherapy or liver or kidney disease. Inattentiveness, indifference, impaired memory, disorientation and disordered perception are common, but the most characteristic signs are ocular. These include nystagmus, lateral rectus palsy (occasionally bilateral), conjugate horizontal gaze palsy or complete ophthalmoplegia. Truncal ataxia is present in 80% of patients and peripheral neuropathy is also common. The amnestic Korsakoff's syndrome frequently emerges after the initiation of treatment and improvement of the acute Wernicke's signs.

Thiamine deficiency is the pathologic source of Wernicke's, but thiamine levels are rarely measured. Instead, decreased erythrocyte transketolase levels and their response to thiamine diphosphate reflect the thiamine deficiency [59]. MRI FLAIR shows high signal intensities in medial thalami, mammillary bodies, periaqueductal gray and tectum of the midbrain [60].

Thiamine supplementation is the mainstay of therapy; however, evidence providing guidance on the most effective dose, route, frequency, or duration of therapy is lacking. Clinical practice guidelines generally recommend an initial regimen of 200-500 mg IV every eight hours. The frequency of every eight hours is based largely on pharmacokinetic considerations as the few published studies largely investigated once daily dosing[61]. The ocular symptoms of Wernicke's improve within few hours to days with administration of thiamine, but the ataxia improves less often.

4.8 Pancreatic Encephalopathy

Pancreatic encephalopathy (PE) occurs in 1.7-35% of patients with acute pancreatitis. It begins within 2 weeks after acute pancreatitis, usually between days 2 and 5, and clinically does not differ from other encephalopathies. Although this entity remains controversial and many believe that can be incorporated within the SAE spectrum (because many of these patients also have signs of sepsis or SIRS), others believe that it entails a different pathophysiology and potentially future treatment options [62]. More specifically, it has been hypothesized that levels of pancreatin (including trypsin, elastin enzyme, lipase and phospholipase A_2) enter the circulation, where activated PLA_2 transforms encephalin and lecithin into highly cytotoxic hemolytic encephalin and hemolytic lecithin [63]. Both damage the BBB, dissolve the phospholipid structure of the cell membrane, hydrolyze mitochondria and cause demyelination and vasogenic edema. PLA_2 also passes through and has potent neurotropism, destroying the phospholipid layers of brain cells, and causing cytotoxic edema. Inflammatory cytokines, which increase after acute pancreatitis and also alter the permeability of the BBB, and systemic disturbances, such as hypoxia, hypotension, disseminated intravascular coagulopathy or fat embolism may also contribute.

There is no clear correlation between the severity of pancreatitis (amylase levels) and the incidence of PE. Higher lipase levels have been reported in the CSF of patients with PE, but this measurement is rarely performed.

There is no specific treatment, only supportive therapy plus thiamine supplementation to avoid development of Wernicke's after prolonged fasting.

4.9 Hyponatremic Encephalopathy

Acute drop of serum sodium concentration (over hours) may lead to seizures or cerebral edema even with levels as high as 125 mEq/L, whereas more chronic sodium decreases (over days) even below 110 mEq/L can be tolerated. Neurons may initially develop edema, but later compensate by shedding solute and water to the extracellular space. In this chronic phase, if sodium is rapidly raised, the cells may shrink causing osmotic demyelination (previously known as central pontine myelinolysis) [50].

The treatment depends on the etiology, acuity and severity of symptoms. Experts' recommendations and European Societies' guidelines have been recently published [64,65]. In hypertonic hyponatremia, treatment focuses on treating the underlying disorder with replacement of estimated salt losses. In hypovolemic hypotonic hyponatremia, normal saline should be given. In hypervolemic hypotonic hyponatremia, free water restriction is instituted. In chronic isovolemic hypotonic hyponatremia, water restriction and/or demeclocycline should be used.

In acute hyponatremia with severe symptoms (e.g., seizures or cerebral herniation), hypertonic sodium can be used with a goal to resolve symptoms and raise sodium by 4-6 mmol/L. Choice of hypertonic sodium agent will vary by institution. A summary of commercially available products is provided in Table 6. In addition to commercially available products, institutions may compound additional concentrations. Thus, local practice may vary greatly. In chronic hyponatremia ($Na^+ \leq 120$ mmol/L for > 48 hours), sodium correction should be limited to 4-6 mmol/L/day. For patients with severe symptoms, the first day's increase can be accomplished during the first 6 hours of therapy, with subsequent increases postponed until the next day. Overall, in chronic hyponatremia, correction should not exceed 8 mmol/L/day, especially in patients at high risk for osmotic demyelination (with $Na^+ \leq 105$ mmol/L or hypokalemia, in alcoholics, malnourished or patients with advanced liver disease) or 10-12 mmol/L over any 24-hour period (and up to 18 mmol/L in any 48-hour period) in patients with normal risk for osmotic demyelination [64]. More complex guidelines follow a similar correction paradigm [65]. Vasopressin antagonists may be used in hypervolemic or isovolemic hypotonic hyponatremias [66]

Table 7:
Comparison of Commercially Available Iso- and Hypertonic Sodium Products Used in the Management of Hyponatremic Encephalopathy

Product NaCl	Concentration (mEq Na/L)	Commercially Available Product Sizes	Equivalent Initial Bolus
0.9%	154	1000 mL	333 mL
1.5%	257	500 mL	200 mL
2%	308	500 mL	150 mL
3%	513	500 mL	100 mL
5%	855	500 mL	60 mL
14.6%	2500	20 mL, 40 mL, 250 mL	20.5 mL
23.4%	4000	30 mL, 100 mL	13 mL

4.10 Hypoglycemic Encephalopathy

Because of the brain's dependence on glucose, severe hypoglycemia with serum glucose values < 40 mg/dL may lead to serious sequelae. The symptom threshold

varies depending on baseline daily glucose levels [67]. Severe hypoglycemia can occur in Type 1 or Type 2 diabetic patients and most commonly is associated with insulin therapy or sulfonylurea overdose.

The neuroglucopenic symptoms and signs associated with either postprandial or fasting hypoglycemia such as cold perspiration, lightheadedness, and tachycardia are due to sympathetic activation and catecholamine secretion. These are followed by global or focal central nervous system dysfunction (headache, confusion, tremor, stupor, seizures) which can mimic stroke. When hypoglycemia becomes severe and prolonged, coma and decorticate or decerebrate posturing from selective brain damage occur. Some brain areas, such as the dentate gyrus of the medial temporal lobe, the superficial layers of the neocortex and the basal ganglia, are more susceptible to injury.

Treatment consists of administration of IV dextrose and often necessitates continuous dextrose infusion. Glucagon administration is also effective and may be underutilized [68]. Hypoglycemia due to sulfonylurea overdose can also be treated with octreotide, a somatostatin analog, that blocks insulin secretion from pancreatic beta cells [69]. Profound and prolonged hypoglycemia, normal or higher body temperature, and a low lactic acid level during hypoglycemia are predictors of a poor outcome [70].

4.11 Hyperglycemic Encephalopathy

Hyperglycemia encephalopathy can occur in the context of diabetic ketoacidosis or, more commonly, with hyperosmolar hyperglycemic state (HHS). Encephalopathy may occur at serum glucose levels > 300 mg/dL in DKA or > 600 mg/dL in HHS. The degree of impairment of consciousness may correlate with the degree of serum osmolality changes. Alterations in electrical activity within the ascending reticular activating system with multiple neurotransmitter derangements, as well as cerebral edema due to fast therapeutic interventions to correct hyperglycemia, have been implicated in the pathophysiology of this encephalopathy [40].

Neurologic signs and symptoms occur more frequently with HHS and progress from confusion and lethargy to stupor and coma. Focal neurologic deficits mimicking stroke or TIA, or hemichorea-hemiballismus (coined as C-H-BG [chorea, hyperglycemia, basal ganglia] syndrome [71]) can also occur with HHS [40]. Additionally, “reflex seizures” due to passive limb movements can also be seen with HHS [72].

Treatment of the severely contracted intravascular compartment with normal saline, IV insulin administration and correction of the profound electrolyte derangements usually improves the encephalopathy.

4.12 Hashimoto's or Corticosteroid-Responsive Encephalopathy

This uncommon syndrome can be found in the literature under various names, including steroid-responsive encephalopathy and associated autoimmune thyroiditis (SREAT) [73] and is more common in women. It is associated with high titers of antithyroid peroxidase (also known as antimicrosomal) or anti-thyroglobulin antibodies. However, their role in the pathogenesis of brain dysfunction is unclear, since they may also be circulating in asymptomatic patients. Other autoantibodies, including anti-neuronal and anti-enolase may play a more significant role, but this is unproven. Cerebrospinal fluid in a large series of patients was positive for anti-thyroid peroxidase antibodies (19%), for anti-thyroglobulin antibodies (4%) or for both (53%) [73].

Patients may have a relapsing-remitting course and present with tremor, stroke-like symptoms, gait ataxia, seizures, myoclonus [74], sleep abnormalities, psychosis or a progressive cognitive decline [75]. Thyroid hormones including TSH may be normal, high or low. EEG shows diffuse slowing, triphasic waves or periodic lateralizing epileptiform discharges (PLEDs).

Characteristically, these patients respond to corticosteroids, either IV methylprednisolone 1 g/day for 5 days or prednisone 60-100 mg/day for 10-30 days [75,76]. However, patients meeting all Hashimoto's criteria without response to steroids have also been reported [75] and 16% may relapse, especially those initially comatose [73]. There may also be an association between higher serum TPO-Ab-titers and favorable outcomes [77].

4.13 NMDA-Receptor and Other Autoimmune or Paraneoplastic Encephalopathies

Over the last decade a large number of patients with limbic encephalitis or refractory seizures have been found to host autoantibodies against intracellular or extracellular neuronal molecules and be associated with tumors (paraneoplastic) or not. The most well-characterized extracellular antibodies are against brain N-methyl-D-aspartate receptors (NMDAR), but others have also been described. These include antibodies against voltage-gated potassium channel complex, including autoantibodies targeting contactin-associated protein-like 2 [CASPR2] [78] or leucin-rich glioma-inactivated 1 protein [LGI1], antibodies against glutamate receptors (GluR1 and 2) in the alpha-amino3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor complex [79], glycine receptors, and GABA A [80] or B [81] receptors. Antibodies against intracellular components, such as glutamic acid decarboxylase (GAD65) [82], Ma1 or Ma2 [83], Hu or CV2/collapsing response mediator protein-5 antineuronal nuclear antigens [84] and amphiphysin [85], have also been described. Not all antibody-mediated encephalopathies present with the acute symptoms of delirium. Often the course is more indolent [85] and, although some show findings of limbic encephalitis on neuroimaging [86], these are

not pathognomonic, and antibodies in both CSF and serum need to be tested, with titers or concentrations correlating with distinct clinical features [87].

In NMDAR encephalitis, antibodies are detected in serum or CSF. Most patients are female (80%) and in most, the presence of these antibodies should be considered a paraneoplastic syndrome. Ovarian teratomas can be found in 26-59% of patients. Only 2% have another type of tumor, usually neuroblastoma or Hodgkin's lymphoma [88]. However, there is another group of antibody-positive patients with encephalopathy without detection of neoplasms despite extensive evaluations [89]. The younger the patient, the lower the chances a tumor will be found [88]. One of the implicated pathophysiologic mechanisms is the increase in the internalization rate of surface NMDAR clusters after antibody binding, leading to decrease in NMDAR-mediated currents (without any evidence of direct blockade of the receptors by the antibodies) [90].

Symptoms and signs of NMDAR encephalitis can be divided into a prodromal, early, and late phase. The prodromal phase is characterized by headache, fever, vomiting, and diarrhea. In the early phase, psychiatric symptomatology, such as anxiety, delusions, paranoia, echolalia or seizures are common. In the late phase, movement disorders, such as choreoathetoid, orofacial movements, myoclonic or oculogyric crises and opisthotonus or autonomic instability with hyperventilation, tachycardia, pyrexia or sialorrhea predominate [91].

Lower initial NMDAR antibody levels and less frequent confusion, agitation, amnesia and reduced consciousness may be found in non-paraneoplastic cases [89].
Patients with LGI1-antibodies have a limbic encephalitis, often associated with hyponatremia. A characteristic presentation in up to 47% of patients, faciobrachial dystonic seizures, can precede the cognitive manifestations by several weeks and the EEG can be negative even during the events [92]. CASPR2 antibodies cause a more variable syndrome and almost exclusively affect older males [93].

CSF in NMDAR encephalitis may initially show a lymphocytic pleocytosis, elevated protein and oligoclonal bands, but in other autoimmune encephalitides, such as LGI1, cell count and protein can be unremarkable in 75% of cases [92]. The diagnosis is made when antibodies are detected in the CSF or serum, although only the CSF may remain positive after treatment. CSF antibodies have higher sensitivity than serum antibodies, and their titers are higher in patients with poor outcomes or in the presence of a teratoma than in patients with good outcomes or no tumor [94]. EEG may show diffuse or rhythmic delta activity or non-convulsive status epilepticus, and MRI is non-diagnostic in the majority (66%) of NMDAR encephalitides. Characteristic hippocampal edema or volume loss, cerebellitis, striatal abnormalities and brainstem encephalitis are more common with other paraneoplastic or autoimmune encephalitides [86]. For example in a recent series of LGI1 antibody encephalitis, hippocampal lesions were seen in 74% of cases, 81% of which were unilateral [92].

The first step in treating these patients is tumor detection and removal, if present [95]. During anesthesia, propofol and sevoflurane should be avoided, and benzodiazepines, opioids and non-depolarizing paralytics should be used instead in order to avoid exacerbation of dyskinesias and seizures [96]. Subsequently, IVIG or plasma exchange and immunosuppression with methylprednisolone will lead to improvement. Rituximab alone [97,98] or plus cyclophosphamide may be considered in the refractory cases (Table 7). Recurrence will eventually mandate chronic immunosuppression in 20-25% of patients with azathioprine or mycophenoloate mofetil [88]. Some may require a prolonged ICU stay and extensive inpatient care [99].

Table 8:
Medical Management for NDMAR

Drug	Dosing	Monitoring	Adverse Effects
IV methylprednisolone	1 gram intravenous daily for 5 days	Blood sugar, fluid status, blood pressure	Hyperglycemia, insomnia, agitation, HPA axis suppression
IV immunoglobulin	0.4 grams/kg daily for 5 days	Renal function, serum electrolytes, CBC, blood pressure, LFTs	Renal failure, venous or arterial thromboembolism, chest pain/tightness, electrolyte abnormalities, aseptic meningitis, hemolytic anemia, PRES
Rituximab	375 mg/m^2 weekly for 4 weeks	CBC with differential, HBV screening, LFTs, pre-treatment with antipyretics and antihistamines	Transfusion related reactions (cardiac arrhythmias, fever, chills), HBV and other viral reactivation, PML, mucocutaneous reactions, anaphylaxis, PRES, hypertension, anaphylaxis
Cyclophosphamide	750 mg/m^2 monthly (given with the 1st dose of rituximab, then monthly)	CBC with differential, renal function, LFTs, electrolytes, fluid balance	Hemorrhagic cystitis, bone marrow suppression, hepatotoxicity, nausea and vomiting, PML

HPA: hypothalamic-pituitary-adrenal axis; CBC: complete blood count; LFTs: liver function tests; PRES: posterior reversible encephalopathy syndrome; HBV: hepatitis B virus; PML: progressive multifocal leukoencephalopathy

4.14 Toxic Encephalopathies

Toxic encephalopathies (TE) are caused by various neurotoxins and are subdivided into legal/illegal drug causes and those from occupational/ environmental agents. There is usually a dose-response and duration exposure relationship between the agent and the severity or reversibility of the

encephalopathy. Benzodiazepines, narcotics, anticholinergic drugs, baclofen and antimicrobials, such as cefepime, ciprofloxacin, metronidazole, or voriconazole, are common iatrogenic etiologies, especially when renal clearance is impaired [62,100]. Cefepime-induced encephalopathy is of special interest for neurointensivists because of its widespread use in ICU patients. Patients can present with impaired consciousness, myoclonus or non-convulsive status epilepticus [101].

Clinically, TE presents as a nonfocal or symmetrical neurological syndrome. Acute diffuse TE is frequently due to exposure to organic solvents or gases (CO, hydrogen sulfide, cyanide) or organic heavy metals (methyl mercury, tetraethyl lead, organic tin). A cerebellar syndrome is seen after methyl mercury (Minamata disease), methyl bromide or dimethyl and trimethyl organic tin intoxications. Parkinsonism is classically seen after manganese, carbon monoxide, carbon disulfide, methanol and cyanide poisoning. A vascular syndrome with multiple cerebral infarctions, coronary artery disease, retinopathy, kidney glomerulosclerosis, parkinsonism and hypertension, associated with atherosclerosis, has been reported with carbon disulfide poisoning [22]. Although many of these clinical syndromes have overlapping features, if there is a clear exposure history, the correct diagnosis may be easily made. If such exposure is unknown or questionable, a detailed clinical exam, together with measured levels or occasional specific neuroimaging findings (e.g., manganese causes bilateral symmetrical increase in signal intensities of the globus pallidus and midbrain on T1-weighted MRI [102]), can lead to the responsible neurotoxin.

5. Nursing Care

As the bedside nurse spends a significant amount of time directly caring for the patient, they must be knowledgeable about toxic metabolic encephalopathies, their potential sequelae, and interventions to care for the patient. This section will address the nursing care and system approaches to several common causes and contributors to encephalopathy; delirium prevention, assessment and treatment and protocol-driven assessment and management of alcohol withdrawal.

5.1 Pain, Agitation & Delirium

Pain, agitation, and delirium identification and treatment in intensive care unit settings have generated substantial research efforts over the last several decades. Delirium, pain and agitation can be difficult to assess independently of each other as symptoms often overlap. Several validated scales are available and should be used to assess patients for pain, agitation and delirium. A stepwise and organized approach to identify who is at risk for delirium, the presence of pain, and level of consciousness (including sedation or agitation) and the presence of delirium improve the recognition and early treatment of delirium [103]. Clinical Practice Guidelines (CPGs) support the routine assessment of patients in the ICU for the presence of pain, agitation and delirium. [26] However, identification of delirium in patients with neurologic disease is challenging due to underlying neurologic

pathology. Additionally, the available screening tools have not been widely validated in the neurocritical care population. [103] Regardless, an organized approach to assessment is still beneficial and the screening tools used should be considered in the context of the patient's neurologic disease. Unit protocols should encourage the prevention of delirium. [104] The strategies to prevent delirium are similar to those employed to treat delirium and will be reviewed in detail below.

Two validated scales are routinely used in the general ICU population to identify delirium: The Confusion Assessment Method for the ICU (CAM-ICU) and the Intensive Care Delirium Screening Checklist (ISDSC). The CAM-ICU evaluates four domains, including acute or fluctuating alteration in mental status, inattentiveness, altered level of consciousness, and disorganized thinking. This tool has only been validated in a handful of neurocritical care patients, including those with acute ischemic stroke and intracerebral hemorrhage. [103] Patients are considered CAM-ICU positive, or positive for the presence of delirium, if they exhibit either acute onset or fluctuating course or inattention and disorganized thinking or altered level of consciousness (Table 8). The ISDSC evaluates for the level of consciousness, attention, disorientation, hallucinations, hyperactivity or hypoactivity, inappropriate speech or mood, sleep or wake disturbances, and symptom fluctuations. [103] Each incorrect item is worth 1 point, and a score of 4 or more is a positive screen for delirium.

Table 9

	Exclusions	Assessment	Scoring
CAM-ICU	many	4 steps (fluctuate, inattention, LOC, disorganized thinking). Decreased LOC part of delirium screen.	Part 1+2 with either 3 or 4 = (+) delirium
ICDS	few	No steps, all 8 criteria get scored (LOC, disorient, hallucination, hyperactivity, hypoactivity, inappropriate speech/mood, sleep/wake disturbances, symptom fluctuation). Decreased LOC, unable to assess delirium.	> 4/8 points = (+) delirium

5.2 Delirium Management: Non-Pharmacologic Approach

After identifying delirium and taking initial steps to identify and reverse any known causes, treatment of delirium includes pharmacological and non-pharmacological interventions. A variety of non-pharmacological interventions have been shown to minimize the occurrence and duration delirium. [105] Simple interventions including grouping of nursing care, frequent reorientation with direct eye contact, giving

patients access to accurate time clocks, maximizing exposure to natural light and preserving normal sleep-wake cycles through sleep protocols when possible are helpful to prevent and manage delirium. Patients should be offered functioning hearing aids and eyeglasses, and nurses should control the surrounding environment (milieu therapy): this includes a designated quiet time with decreased stimulation and scheduled decrease of noise and lights when appropriate.

Targeted sensory stimulation such as soothing music or age-appropriate television shows may reduce pain and anxiety, cultivate relaxation, and improve mood and movement. [104] However, a recent practice survey in neurocritical care revealed a large practice variance in the use of music and television as a therapeutic intervention.[106] Additional research is needed to explore music therapy as a therapeutic intervention. Restraint use in the agitated or delirious patient and those at risk for delirium should be avoided as physical restraints are associated with higher incidences of delirium.[104,107] If all other options are explored and restraint use is deemed necessary, one should offer the least restrictive restraint and provide more supervision if possible.[108]

Family presence and involvement is increasingly recognized as important in preventing post-intensive care unit syndrome (PICS) and increasing patient safety while in the ICU. [109] Limited research exists on the impact of family involvement in delirium incidence or management. Family and/or family surrogate presence and engagement have increased over the last decade, with movements towards open visitation, involvement in multidisciplinary rounds, and shared decision-making.

Early mobility should also be considered a priority non-pharmacological intervention, since it decreases the duration of delirium and is associated with improved functional recovery for patients with delirium [26,110] Early mobility protocols provide criteria to quickly return a patient to their prehospital abilities as patients meet defined physiologic criteria. These include systemic safety parameters that span the spectrum and intensity of critical illness. These stepwise protocols safely advance activity from passive range of motion to ambulating.[105] Successful mobility protocols require a culture of teamwork, particularly when the patient is in an altered state with catheter management and assistive devices.[111]

While initial studies of early mobilization excluded patients with neurocritical care illnesses, recent publications suggest this intervention may be safe and effective in the Neuro ICU too. Olkowski and Shah [112] provide a neuro-specific safety checklist to consider patients for early mobilization in the Neuro ICU. Brissie, et al. [110] created a neurointensive care unit-specific protocol for early mobility that progresses in a detailed, stepwise approach starting with passive range of motion and ending with ambulation. Klein, et al. [113] found that an early mobility protocol within the neurological intensive care unit increased the mobility and discharge home status while decreasing the length of stay, blood stream infections and hospital acquired pressure ulcers (HAPU). While patients treated with this protocol exhibited higher depression scores, their hostility and anxiety scores decreased

with mobility. These studies suggest that nurse-driven early mobility protocols can be successfully implemented in the neurocritical care patient population.

The promotion of sleep with development of day and night routines mimicking the circadian rhythms aids in the reduction of delirium. Manipulating the environment for organized awake times with the lights on, blinds open, personal care and therapeutic activities during these awake times can be achieved. [26] Organized quiet time to decrease noise and light stimulation and avoiding nonessential activities during protected sleep times also improves sleep quantity. [106,114] If interventions are necessary overnight, clustering the interventions to minimize sleep interruptions is advisable. [104] While clustering intervention to improve sleep opportunities is ideal, this should not be at the expense of pain assessment and treatment, as under-treatment of pain will impede the restorative, deeper sleep stages. [105] Ear plugs and sleep masks, as part of a sleep hygiene bundle or in isolation, have also been proven effective in delirium reduction. [115,116]. Finally, while frequent neurologic assessments are a key part of nursing care in the Neuroscience ICU, they disrupt sleep and this practice warrants discussion and critical examination in patients with prolonged ICU stays. [117] An attempt to synchronize nursing assessment with physicians and decrease the interruptions of sleep and rest should be the goal.

The Society of Critical Care Medicine (SCCM) ICU Liberation Project (often termed the ABCDEF bundle **A**ssess, prevent, and manage pain, **B**oth the spontaneous awakening trials and spontaneous breathing trials the **C**hoice of analgesia and sedation; assess, prevent, and manage **D**elirium, **E**arly mobility and **E**xercise; and **F**amily engagement and empowerment) incorporates a number of interventions aimed at minimizing the occurrence of delirium and increasing the identification of delirium when present.[105] Many of the ICU liberation assessments and interventions can be developed into hospital protocols that are driven by the bedside nurse. While the ICU liberation project has increased in popularity and been shown to improve patient outcomes, widespread adaption and adherence is suboptimal. [28] The ICU liberation ABCDEF bundle, however, has not been widely studied in the neuroscience patient population and additional research is needed to understand how the bundle should be tailored for this patient population.

Bedside nurses should routinely evaluate patients for the presence of pain, either by self-report or via assessment scores known for their reliability and validity, such as the Behavioral Pain Scale (BPS) or Critical Care Pain Observation Tool (CPOT). Pain should be managed before sedation is escalated (SCCM guidelines). The Richmond Agitation Sedation Scale (RASS) and Sedation Agitation Scale (SAS) provide subjective assessment information on sedation and agitation. Both require education and acceptance of nursing staff for success. [118]

5.3 Alcohol Withdrawal

Assessing the extent of baseline alcohol consumption and risk for withdrawal is challenging in the ICU population. Often, critically ill patients are unable to provide a history of alcohol consumption. Alcoholic screening tools such as the CAGE questionnaire, the Michigan Alcoholism Screening Test, the Alcohol Use Disorders Identification Test (AUDIT), the AUDIT-C, and the Audit-PC identify the Alcohol Use Disorder (AUD) but have not been validated within intensive care populations. [119] The Clinical Institute Withdrawal Assessment for Alcohol Withdrawal (CIWA-Ar) is often used to assess alcohol withdrawal in the ICU, but has not been validated for the critically ill. However, this assessment tool is still often used and may provide additional data to manage a patient in alcohol withdrawal.

Assessment and management of alcohol withdrawal in the patient with neurologic illness presents unique challenges. Clinical signs and symptoms of the critical illness and those of withdrawal may be confused or underappreciated, and may delay appropriate treatment. [119] Thorough and astute nursing assessment, attentive monitoring of subtle differences within the patient condition, and clinical judgment are pivotal in determining differences between the critical illness and alcohol withdrawal. [119,120] Early detection of emerging alcohol withdrawal could stop the progression of the symptoms to delirium tremens. However, worsening symptoms in a patient with known alcohol use should not be assumed to be always withdrawal-related. Patients with known alcohol use and symptoms of withdrawal should be closely monitored for seizures[119], which in the Neuro-ICU may also be due to intracranial pathology.

The mainstay of alcohol withdrawal treatment is the administration of benzodiazepines, with the addition of supplemental agents including phenobarbital, dexmedetomidine, and propofol.[120] Nurse-driven protocols that guide the administration of medication based on assessed withdrawal symptoms is associated with faster time to symptom control and with decreased sedative medications use and tracheostomy rates. [121,122] However, these studies need to be replicated in the neurocritical care patient population. Even with protocols, care should be individualized to the specific patient situation and always be interdisciplinary.[120]

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