ERABI EVIDENCE-BASED REVIEW of moderate to severe ACQUIRED BRAIN INJURY

Clinical Guidebook

8. Acute Interventions for Acquired Brain Injury

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Acute Interventions for Acquired Brain Injury

By the end of this chapter you should know:

- How to recognize acute acquired brain injury complications
- The acute interventions supported by guideline groups
- The common assessments and outcomes used to evaluate acute complications of ABI
- Diagnostic criteria for acute complications
- How to explain a possible pathway of care for an individual with acute complications following an ABI

8.1 Introduction to Acute Interventions

During the initial stages of an Acquired Brain Injury (ABI) irreversible damage to the central nervous system occurs, commonly known as the primary injury. Subsequently, the increased edema, release of toxic amounts of excitatory neurotransmitters, and impaired ionic homeostasis caused by the primary injury mediate ongoing damage to the brain, causing sequelae such as intracranial hypertension, brain ischemia and potential brain herniation— a group of complications commonly referred to as secondary injury (Werner & Engelhard, 2007). Considering primary injury occurs immediately upon insult and is irreversible, acute ABI treatment focuses on preventing or minimizing the extent of secondary injury.

A large variety of modalities are available and have been implemented in the acute phase post ABI (<14 d) with the goal of reducing mortality and improving long-term functional outcomes. These interventions will be broadly classified in this guidebook based on their therapeutic goal: reducing elevated intracranial pressure (ICP), improving emergence from coma, or improving long-term morbidity and mortality outcomes. Unfortunately, for a large number of the interventions reviewed conflicting evidence exists regarding their therapeutic effect. Heterogeneity in ABI populations, mechanisms of injuries, and treatment protocols have all contributed to the diversity of study results despite the implementation of seemingly identical interventions. As a result, lack of consensus on the effectiveness of an intervention appears to be the norm rather than the exception (Lei et al., 2013). Despite the lack of unanimity in the field, a large number of clinical guidelines have been created with the goal of standardizing care in their respective region, and improving mortality and long-term outcomes (Cnossen et al., 2016; Gupta et al., 2016). Following recommendations from those guidelines, as well as authors of meta-analysis, the movement to provide higher level of evidence for acute ABI interventions has yielded a higher number of RCTs in the last 10 years (Alali et al., 2017; Alarcon et al., 2017). As a result, the field is being provided with an influx of new, higher level evidence from which to bolster our understanding of the therapeutic effects of acute interventions.

The purpose of this guidebook is to combine the examined literature in ERABI (Module 15: Acute Interventions), with clinical consensus, and recognized guidelines in order to provide evidence-based strategies for the management of Moderate to Severe ABI in the acute phase. The authors of this work recognize that there are other parameters and factors that must be monitored and influence acute care post ABI that are not discussed in this guidebook. As such, this guidebook does not provide an exhaustive list of all interventions, parameters monitored, or assessment tools used in acute case of moderate to severe ABI.

8.2 Clinical Presentation

Q1. What are the most commonly used monitoring indicators during the acute phase of ABI?

1. Pupil size and reactivity
2. Glasgow Coma Scale score <8
3. Herniation

In reality, the most commonly used indications for monitoring in the acute phase of moderate to severe ABI include pupil size and reactivity, Glasgow Coma Scale (GCS; particularly motor), CT for signs of herniation, and if monitoring ICP then an ICP monitor (Chesnut et al., 2012).

Additionally, a patient's altered level of consciousness, indicated by GCS score, can serve as a tool to monitor neurological status. In light of the fact that most patients with moderate to severe ABI (GCS<12) lack reliable eye movements and are often intubated, preventing the assessment of vocal scores, motor GCS score is often relied upon as an indicator of functionality.

8.2.1 Intracranial Hypertension

Q2. What is the commonly accepted threshold for elevated ICP?

1. ICP ≥ 20mmHg

High ICP, generally accepted as ICP ≥ 20mmHg, is one of the most common causes of death and disability following severe ABI (Werner & Engelhard, 2007). Under conditions of gradual volume increase, the brain is able to accommodate by displacing cerebrospinal fluid (CSF) and venous blood into the spinal canal, thus maintaining a fixed intracranial volume; this is known as the Monro-Kellie hypothesis with an appropriate ICP of 0-15 mmHg (Dunn, 2002; Fantini et al., 2016). However, the rapid accumulation of edema or formation of a mass lesion (i.e., hemorrhage) in the intracranial compartment following an ABI overwhelms the capacity of the brain to accommodate, resulting in the rapid increase of ICP (Carney et al., 2017; Vella et al., 2017). Subsequently, once a critical volume is reached the brain is unable to expand further, resulting in larger changes in ICP with smaller changes in volume. These changes leave the brain extremely vulnerable to secondary ischemia due to diminished cerebral perfusion, and if pressure continues to increase, brain herniation (tonsillar/tentorial) may occur potentially resulting in death (Carney et al., 2017; Sahuquillo & Arikan, 2006; Vella et al., 2017).

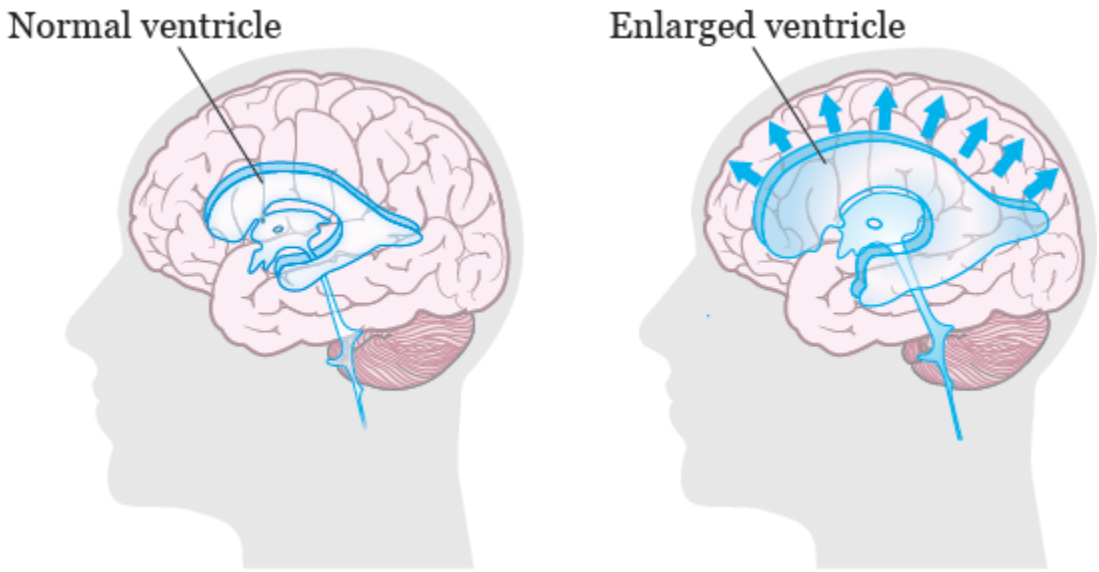

Figure 8.1 An illustration showing normal ventricular pressure compared to increased ventricular pressure and the forces exerted onto the brain tissue by this complication.

The clinical presentation of intracranial hypertension is complicated by the fact that classical signs and symptoms of raised ICP (i.e. morning headache, papilloedema, and vomiting) or signs of brain ischemia (neurological deficits such as those seen in stroke patients) are virtually impossible to assess given the patient's altered level of consciousness and/or the potential masking of signs due to sedation, paralysis, or intoxication (Dunn, 2002; Hlatky et al., 2003; Maas et al., 2008).

In more severe ABI cases, patients may present with signs of brain herniation secondary to increased ICP such as impaired pupillary dilation, pupillary reactivity, ptosis, impaired up gaze, increased blood pressure, pulse, and respiratory changes (Dunn, 2002; Jennett & Stern, 1960; Stevens et al., 2015). Generally, signs of herniation progress in order of ipsilateral pupillary dilation and contralateral hemiparesis, bilateral pupillary dilation, respiratory depression, blood pressure dysregulation, and altered cardiac rate serving as the last signs before impeding brain death (Jennett & Stern, 1960; Stevens et al., 2015).

8.2.2 Coma/Disorders of Consciousness

Consciousness can be defined as the state of awareness of self and the environment and is comprised of two interconnected components: arousal and awareness. Arousal is defined as wakefulness or vigilance; and is centralized in the Ascending Reticular Activating System (ARAS) region of the midbrain and the pons. Awareness is the knowledge of self and environment; primarily associated with higher cortical structures (Giacino et al., 2018; Plum, 1991; Seel et al., 2010; Zeman, 2006). Injury to any of these pathways or areas of the brain can result in impaired consciousness and the presentation of Disorders of Consciousness (DOC).

Altered level of consciousness is a core finding of moderate to severe ABI, as GCS score is used to categorize and define the extent of brain injury (Middleton, 2012; Teasdale et al., 2014). In moderate traumatic brain injury (TBI; GCS 9-12), patients are more likely to present as lethargic, whereas in severe ABIs (GCS ≤8), the patient is likely to be comatose (McKee & Daneshvar, 2015). Multiple studies have observed the relationship between initial GCS score and prognosis, noting lower scores as a strong

predictor for worse long-term morbidity and mortality outcomes (Maas et al., 2008; Skandsen et al., 2010; Stein et al., 2010; van Dijck et al., 2018).

As previously mentioned, patients with severe ABI may present in a comatose state. Patients in a coma present with a distinct lack of awareness and arousal, and an absence of eye opening and sleep/wake cycles (Seel et al., 2010). Recovery from a coma for patients with ABI is variable, with some patients progressing rapidly through the continuum of Unresponsive Wakefulness Syndrome (previously known as vegetative state), to a Minimally Conscious State (MCS), and eventually full recovery (Giacino et al., 2018). However, recovery in other patients may take months-years and may halt at any stage with no further progress (Bruno et al., 2011). Accurate diagnosis of a specific DOC is of utmost importance as different disorders have been found to be associated with different prognosis and treatment protocols (Lammi et al., 2005) (Giacino & Kalmar, 1997; Giacino et al., 2018). As such, groups have made significant efforts to set out distinct diagnostic criteria and treatment protocols for the different DOCs, clinical presentations of differing DOCs are presented below. Please note that the Diagnostic criteria for DOCs are discussed in section 8.4.2.

Table 8.1 Clinical presentation of Disorders of Consciousness

Disorder of Consciousness	Characteristics
Coma	• Absence of spontaneous eye opening • Absence of sleep/wake cycles • Complete absence of responses to stimuli
Unresponsive Wakefulness Syndrome	• State of arousal without awareness • Recovery of spontaneous eye opening • Autonomic function sufficient to support cardiorespiratory function
Minimally Conscious States (MCS)	• Arousal with minimal but definitive awareness (to self or environment) • Conscious behaviours inconsistent, must be differentiated from reflexive movements

8.3 Outcome Measures and Clinical Assessments

Although there are numerous tools and measures available to assess individuals throughout the recovery process post ABI, only one clinical assessment tool and four outcome measure tools will be discussed in this section. Considerations for the use of each tool, as well as how to access each assessment are also discussed.

8.3.1 Clinical Assessment

8.3.1.1 Glasgow Coma Scale

The GCS was created in 1974 as a way to effectively communicate a patient's level of consciousness in a standardized and objective manner. The scale is freely available online here.

The GCS consists of three sections, each assessing consciousness and severity of injury through a different domain: eye movement (scored from 1-4), verbal response (scored from 1-5) and motor response (scored from 1-6). Each section is scored individually, with the highest cumulative score possible being 15, representing a normal and alert patient. The lowest cumulative score is 3, representing the worst possible outcome and a patient who is comatose.

Clinical Tip!

For more information on conducting the GCS and eliciting responses click here https://www.glasgowcomascale.org/what-is-gcs/

The scale serves not only to define the severity of the brain injury, but it can also be used to monitor neurological status across a range of conditions (Middleton, 2012; Teasdale et al., 2014). Further, initial GCS score has been found to be strongly correlated with morbidity and mortality outcomes, as lower values represent worse outcomes (Maas et al., 2008; Skandsen et al., 2010; Stein et al., 2010; van Dijck et al., 2018).

A limitation of this outcome measure is that patients may be intubated or sedated/intoxicated on admission, impairing the use of the scale (Middleton, 2012). It should be noted that pupillary reaction and dilation, another important diagnostic factor in ABI, is not directly assessed by the GCS. The latter has spurred the development of the GCS-P, a modification of the original scale including pupillary reactivity for a more comprehensive assessment of brainstem function.

Component Tested	Score
Eye Response	
Eyes open spontaneously	4
Eye opening to verbal command	3
Eye opening to pain	2
No eye opening	1
Motor Response	
Obeys command	6
Localises pain	5
Withdraws from pain	4
Flexion response to pain	3
Extension response to pain	2
No motor response	1
Verbal response	
Orientated	5
Confused	4
Inappropriate words	3
Incomprehensible sounds	2

Figure 8.2 The Glasgow Coma Scale

8.3.2 Outcome Measures

8.3.2.1 Glasgow Outcome Scale (Extended)

The Glasgow Outcome Scale (GOS), designed by Bryan Jennett and Michael Bond to compliment the GCS, is the most frequently used tool to assess functional outcomes in patients post ABI (McMillan et al., 2016). The assessment tests areas such as emotional control, cognitive function, and physical abilities in the context of pre-injury abilities and post-injury environment (McMillan et al., 2016). The assessment is usually administered after discharge (3, 6, and/or 12 mo.) (Wilson et al., 1996), and groups individuals into 5 categories: 1) Death, 2) Vegetative State, 3) Severe Disability, 4) Moderate Disability, 5) Good Recovery. The higher the value on the scale, the better the outcome.

The scale has undergone multiple changes, including the addition of 3 more segments to the original GOS to further stratify outcomes. The GOS-E is available here. All versions of GOS forms are freely available online.

The most commonly used versions, GOS and GOS-E, have high levels of inter-rater reliability (GOS, kappa=0.89; GOS-E, kappa=0.85) and benefit from the ability to conduct the survey both with an assessor in person or over the phone, as well a postal version to be completed by the patient (or a proxy) (McMillan et al., 2016).

8.3.2.2 Functional Independence Measure

The Functional Independence Measure (FIM) is a tool to assess the quality of life of patients with a disability. Primarily, the FIM analyzes the functional independence of patients through assessment of various physical and cognitive domains (Uniform Data System for Medical Rehabilitation, 2012). The FIM is composed of 18 items, 13 of which assess motor (eating, grooming, bathing, dressing, toileting, bowel and bladder control, transfers and locomotion) and five which assess cognitive (communication and social cognition) function. Each item is ranked from 1 – 7 (1= total assistance to complete task and 7= total independence). The lower the score, the more dependent a patient is for that particular task.

The FIM requires a trained assessor to administer it, on average lasting approximately 15-20 minutes per assessment (A license to use the FIM instrument may be obtained at www.udsmr.org). The FIM can be used to guide discharge decisions, or to objectively quantify the progress an intervention or rehabilitation program is making in a patient's recovery. The FIM further provides benchmarks that assessors can use to compare patient progress to, as there exist standardized charts outlining expected function for different disability patterns (i.e., brain dysfunction, spinal cord dysfunction, stroke rehabilitation, etc.).

The FIM has reported high interrater reliability (0.95), test-retest and equivalence reliability (0.95, 0.92 respectively; (Ottenbacher et al., 1996), and internal test reliability (α=0.93-0.95, (Dodds et al., 1993).

8.3.2.3 Disability Rating Scale

The Disability Rating Scale (DRS) is a tool created to accurately measure functional changes in patients post TBI. The DRS addresses all 3 stages of the World Health Organization health disorders— impairment, disability and handicap—and as such can be used throughout the entire patient recovery process (Barbotte et al., 2001; Hammond et al., 2001).

The DRS examines eight areas of functioning in four discrete categories: consciousness (eye opening, verbal response, motor response), cognitive ability (feeding, toileting, grooming), dependence on others, and employability. Each category is graded on a scale of 0-3 or 0-5, with a total maximum score of 29. The greater the level of disability the higher the score, with 29 representing an extreme vegetative state and a score of 0 representing no impairment (Shirley Ryan Ability Lab, 2019; Wright, 2000).

The test can be performed by any observer who has read the article/manual and takes approximately 5-30 minutes to complete- depending on the familiarity of the observer with the scale and the current condition of the patient. The scale is free to access here.

Some of the strengths of this scale include its specificity to patients with brain injury, as well as its ability to be used from the very beginning of the recovery process up to years post discharge. Additionally, the DRS has excellent test/retest reliability (r=0.95; Gouvier et al., 1987), interrater reliability (r=0.97-98; Rappaport et al., 1982), and internal consistency [Cronbach's alpha for original DRS (0.84), DRS- Post acute interview (0.82)].

8.3.2.4 Ranchos Los Amigos Scale

The Ranchos Los Amigos Scale (RLAS) is an assessment tool used to evaluate level of awareness, cognition, behaviour and interaction with the environment (Lin & Wroten, 2019; Whyte, 2011). Originally developed to assess a patient's cognitive function when emerging from a coma, it is now used in conjunction with the GCS on initial assessment, and also as a tool to monitor progression and neurological status throughout the recovery process. The scale accounts for the current state of consciousness, as well as reliance on any assistance to carry out cognitive and physical functions (Lin & Wroten, 2019).

The RLAS is a single item rating scale with eight levels, each with cognitive and behavioural items that can be recorded as being either present or absent during observation. The lowest value on the scale is 1 ("no response", or coma) and the highest is 8 ("purposeful, appropriate response"). The assessment takes only a few minutes to complete, and can be performed by anyone with little required training.

The strength of this scale lies in its ability to be utilized at the onset of injury and continually throughout the recovery process. In addition, the RLAS is a free tool to access and a link has been provided here. The scale has been recommended for use by multiple associations, including American Physical Therapy association's Traumatic Brain Injury Taskforce (TBI EDGE). Further, the RLAS scale has been proven to have high test-retest reliability (Spearman rho=0.82), and Inter-rater reliability (Average Spearman rho= 0.89; Gouvier et al., 1987).

Criticisms of the scale revolve around the fact that it did not accurately reflect the cognitive status of individuals with higher levels of function (Whyte, 2011). This limitation has since been addressed, and the scale extended to ten items to best reflect different levels of recovery (Stenberg et al., 2015; Whyte, 2011).

8.4 Criteria for Diagnosis

8.4.1 Cerebrovascular Thresholds

As discussed in the intracranial hypertension section, normal ICP lies between 0-15 mmHg (Dunn, 2002; Fantini et al., 2016). While there is no clear consensus on what constitutes "intracranial hypertension", a number of groups have suggested a definition of ≥ 20mmHg within any intracranial space including the subdural, intraventricular, extradural, or intraparenchymal compartments (Sahuquillo & Arikan, 2006). It is important to note that ICP should not be the only value considered during treatment, but rather should be interpreted in the context of brain perfusion and Cerebrovascular Autoregulation (CA) status. By extension values such as Cerebral Perfusion Pressure (CPP), Mean Arterial Pressure (MAP), and cerebral blood flow should be considered (Dunn, 2002; Koskinen et al., 2014). As a result, ICP values below the hypertensive range but still above normal can be tolerated as long as appropriate cerebral blood flow/oxygenation is being achieved (Carney et al., 2017).

CPP, the driving pressure responsible for cerebral blood flow, has an ideal target range of 60-70 mmHg in individuals. The optimal pressure in which to maintain an individual, CPP Optimal (CPP_{opt}), is determined primarily by the patient's CA status (Koskinen et al., 2014; Needham et al., 2017). Individuals with preserved CA would benefit from higher CPPs whereas those with impaired CA, as is often seen in post TBI, would require lower CPPs to prevent the aggravation of vasogenic edema due to increased hydrostatic capillary pressure (Carney et al., 2017; Czosnyka et al., 2001; Koskinen et al., 2014). Lending support to this theory are reports that patients managed at CPP values below CPP_{opt} have higher rates of mortality, whereas those managed with CPP values above CPP_{opt} are more likely to develop negative long-term neurological outcomes and respiratory complications such as Acute Respiratory Distress Syndrome (Aries, 2012; Colton et al., 2014; Depreitere et al., 2014; Needham et al., 2017; Steiner et al., 2002).

Clinical Tip!

For more information on calculating cerebral autoregulation see:
Fantini, S., Sassaroli, A., Tgavalekos, K. T., & Kornbluth, J. (2016). Cerebral blood flow and autoregulation: current measurement techniques and prospects for noninvasive optical methods. *Neurophotonics*, *3*(3), 031411.

Finally, systemic blood pressure control plays a critical role in the management of patients post TBI. Mostly discussed in the context of hypotension, numerous studies have found associations with low systolic blood pressure (SBP< 90 mmHg) and poorer morbidity and mortality outcomes (Lenartova et al., 2007; Manley et al., 2001; Nicholls et al., 2006). There is more uniformity in terms of ideal Systolic blood pressure when compared to CPP, as hypotension negatively affects both people with intact CA, through cerebral vasodilation and subsequent increase in ICP, and those with impaired CA, primarily through cerebral hypoperfusion and subsequent ischemia (Carney et al., 2017; Koskinen et al., 2014). Lately, large groups have begun to reconsider the definition of hypotension in patients with ABI, arguing for a higher threshold (SBP< 110 mmHg) in order to produce better patient outcomes (Berry et al., 2012; Carney et al., 2017).

The Brain Trauma Foundation outlines specific parameter thresholds that should be followed in order to provide patients with TBI with the best possible outcomes (Carney et al. 2017):

ICP: Treating ICP≥ 22 mmHg is important, values above this increase mortality (Level IIB evidence).

CPP: Target range 60 mmHg≤ CPP ≤70 mmHg, depending on patient autoregulatory value (Level IIB evidence)

SBP: Patients 50-69 yrs ≥100 mmHg, 15-49, ≥110 mmHg (Level III evidence).

8.4.2. Coma and Disorders of Consciousness

Screening for DOC should not be conducted until approximately 4 weeks post-injury, this allows confounding factors such as other acute complications, sepsis, and sedating medications to resolve before assessment (Multi-Society Task Force on PVS, 1994).

The criteria for the diagnosis of DOCs have been set forth by groups such as The American Congress of Rehabilitation Medicine (Seel et al., 2010), American Academy of Neurology (Multi-Society Task Force on PVS, 1994), and The Aspen Workgroup (Giacino et al., 2002; Giacino & Zasler, 1995). These criteria are well accepted and have been supported by groups such as the American Academy of Neurology DOC practice guidelines (Giacino et al., 2018).

Table 8.2 Diagnostic criteria for Disorders of Consciousness

Level of Consciousness	Criteria
Coma (Seel et al., 2010)	• Eyes remain continuously closed • Absence of sleep/wake cycles • Purposeful responses to environmental stimuli cannot be elicited • Behaviour limited to reflexive activity
Unresponsive Wakefulness Syndrome (Multi-Society Task Force on PVS, 1994)	All 3 criteria must be met to establish diagnosis: 1) No evidence of sustained, reproducible, purposeful or voluntary behavioural responses to visual auditory, tactile, or noxious stimuli *Note: spontaneous movement, vocalization or facial expressions may be present, but never in the context of meaningful environmental interaction.* 2) No evidence of language comprehension or expression 3) Intermittent wakefulness manifested by the presence of sleep/wake cycles (ie. Periodic eye opening)
Minimally Conscious States (MCS; Giacino et al., 2002; Giacino & Zasler, 1995)	Must be clear and reproducible evidence of 1 or more of the following: 1) Simple command following 2) Gesture or verbal yes/no responses (regardless of accuracy) 3) Intelligible verbalization 4) Movements or affective behaviours that occur in contingent relation to relevant environmental stimuli and are not attributable to reflexive activity. Examples include: A. Episodes of crying, smiling, or laughter in response to the linguistic or visual content of emotional but not neutral topics or stimuli. B. Vocalizations or gestures that occur in direct response to the linguistic content of comments or questions. C. Reaching for objects that demonstrates a clear relationship between object location and direction of reach. D. Touching or holding objects in a manner that accommodates the size and shape of the object. E. Visual pursuit or sustained fixation that occurs
Emergence from MCS Aspen group (Giacino et al., 2002)	Reliable demonstration of either: 1) Interactive communication *Yes/No responses to at least 6 situation orientation questions* *Communication may occur through verbalization, gesture, or assistive technology* 2) Functional object use *Appropriate use of 2 different items on at least 2 different occasions*

8.5 Acute Interventions for Acquired Brain Injury

Interventions used to treat acquired/traumatic brain injuries during the acute (<14 days14d) period can be classified based on their main therapeutic goal: to decrease ICP, hasten emergence from coma, or improve morbidity/mortality outcomes. Within each class, there exists some combination of non-pharmacological, pharmacological, and surgical modalities used to achieve the desired outcome. The sections below outline a combination of the literature reviewed, relevant guideline recommendations and clinical consensus provided by practitioners in the field. Although not all interventions are discussed here, a complete review of the literature can be found in Module 15 (Acute Interventions for ABI) in ERABI.

Click here to access the complete ERABI module on Acute Interventions

8.5.1 Intracranial Pressure Management

As previously mentioned in the Clinical Presentation section of this guidebook, elevated ICP secondary to edema, mass lesions, or hemorrhage can have a devastating effect post ABI. The ischemic environment created by the occlusion of cerebral vessels can impair focal or global circulation in the brain, depending on the insult, resulting in hypoxia and cell death (Doyle et al., 2001). Although there's no consensus on what constitutes "elevated" ICP, a range between 20-25 mmHg has been adopted as the threshold which should be corrected post ABI.

Q3. What are the goals of non-surgical ICP interventions?

1. Reducing cerebral edema
2. Decreasing metabolic demand
3. Maintaining adequate cerebral blood flow

Currently there are two broad categories of therapies used to alleviate increased ICP in patients with TBI; surgical and non-surgical (medical) interventions (Rabinstein, 2006; Vella et al., 2017). Non-surgical therapy focuses on reducing cerebral edema, decreasing metabolic demand, and maintaining adequate cerebral blood flow, and includes the use of both pharmacological agents (diuretics, corticosteroids, barbiturates, etc.) and non-pharmacological interventions (hypothermia, hyperventilation, head posture, body rotation). Conversely, surgical therapies employ physical interventions to reduce ICP by either decreasing the volume of fluid (blood, CSF) or increasing the size of the cranial compartment- i.e., decompressive craniectomy (Vella et al., 2017).

Conflicting evidence regarding the efficacy of certain interventions exists in the ICP literature, making the development of concise guidelines or treatment algorithms difficult. However, the lack of consensus in the literature has not discouraged groups from creating thorough guidelines based on available evidence and regional expertise. Groups like the Brain Trauma Foundation (Carney et al., 2017), the American Academy of Neurology (Giacino et al., 2018), the French Society of Anesthesia and Intensive Care Medicine (Geeraerts et al., 2018), and the English National Institute for Health and Care Excellence (National Clinical Guideline Centre, 2014) have all published guidelines to direct best-care practices for patients with moderate-severe ABI in their region. Although no specific algorithm has been published by these groups, they generally agree with the principle of using non-invasive (pharmacological or

nonpharmacological) interventions as first-line therapies, and reserving surgical interventions for specific indications; i.e., ICP refractory to standard therapy or to evacuate mass lesions.

8.5.1.1 Non-Pharmacological Interventions

Head elevation

Q4. What angle of head elevation has been found to be optimal for reducing ICP?

1. None. To date, evidence for all angles of head elevation is limited, and/or inconclusive. Additionally, no guideline groups to our knowledge make definitive conclusions regarding the use of head elevation.
2. However, head elevation is used within clinical settings regularly with an elevation of 30°.

Overall, there is conflicting evidence that head elevation decreases ICP post ABI. The most commonly tested elevation, 30°, has conflicting evidence regarding its efficacy in both lowering ICP and elevating CPP. Interestingly, studies investigating head elevations both higher (45°,60°) and lower (15°) than 30° have provided (limited) evidence of lowering ICP, suggesting that ICP reduction is not correlated to the angle of head elevation (Ledwith et al., 2010). Furthermore, there's evidence that any head elevation above 10° can predispose an individual to a decrease in MAP, placing a patient at risk of developing hypotension and subsequent cerebral hypoperfusion (limited evidence; Mahfoud et al., 2010; Rosner & Coley, 1986; Schneider et al., 1993).

In accordance with our findings, a recent Cochrane review (Alarcon et al., 2017) analyzing head elevation and ICP refrained from making conclusions on the effects of head elevation, citing poor quality of evidence and study design as the main reasons. **Currently, neither the Brain Trauma Foundation (Carney et al., 2017), National Institute for Health and Clinical Excellence (NICE; National Clinical Guideline Centre, 2014), or the Management of severe traumatic brain injury guidelines (Geeraerts et al., 2018) make any recommendation regarding head elevation to lower ICP, however its effects are supported in daily clinical use.**

Hypothermia

Q5. When is the use of hypothermia recommended and NOT recommended?

1. Hypothermia may be used within 2.5 hours of injury and for no more than 48 hours post-injury in an attempt to decrease ICP.
2. Prophylactic hypothermia is NOT recommended.

A Cochrane review by Lewis et al. (2017) concluded that: *"Despite a large number of studies, there remains no high-quality evidence that hypothermia is beneficial in the treatment of people with TBI. Further*

research, which is methodologically robust, is required in this field to establish the effect of hypothermia for people with TBI".

Strong evidence exists for the support (Smrcka et al., 2005; Zhao et al., 2011) and rejection (Clifton et al., 2001; Andrews et al., 2015) of the use of therapeutic hypothermia in patients post ABI. Notably, the largest studies also reported increases in complications, poorer functional outcomes (GOS-E scores) and increased mortality. A final consensus between the authors concludes that there is strong evidence that hypothermia increases the risk of complications, such as pneumonia.

Key Study

Author/Year/ Country/ Study Design/N	Methods	Outcomes
Zhao et al. (2011) China RCT PEDro=6 N=81	**Population:** TBI; *Treatment Group (TG, n=40):* Mean Age=36.9yr; Gender: Male=29, Female=11; GCS: 3-5=15, 6-8=25. *Control Group (CG, n=41):* Mean Age=37.5yr; Gender: Male=30, Female=11; GCS: 3-5=16, 6-8=25. **Intervention:** Participants were randomly assigned to receive hypothermia (33°C, TG) or normothermia (37°C, CG) for >72 hr. Temperature was lowered using a semiconductor blanket. Outcomes were assessed at 3mo and physiological measures were monitored during treatment. **Outcome Measures:** Glasgow Outcome Scale (GOS), Intracranial Pressure (ICP).	1. Good outcome (GOS≥4) was significantly higher in the TG than in the CG (75% versus 51%, p=0.038). 2. Death was higher in the CG than in the TG (10% versus 3%) but the difference was not significant (p>0.05). 3. After adjusting for age, GCS, and ICP, hypothermia was an independent predictor of good outcome (RR=4.9, p<0.05). 4. Mean ICP was significantly lower in the TG than in the CG at 24 hr (p<0.01) and 72 hr (p<0.01) after treatment.

The Brain Trauma Foundation guidelines (Carney et al., 2017) provide Level IIB evidence that early (within 2.5 h), and short-term (48 h post-injury) prophylactic hypothermia is NOT recommended to improve outcomes in patients with diffuse injury. The Management of severe traumatic brain injury (Geeraerts et al., 2018) and NICE guidelines (National Clinical Guideline Centre, 2014) have made no recommendations on the use of hypothermia post TBI.

Overall, these guidelines do not recommend the use of hypothermia as a first-line intervention for lowering ICP or improving long-term outcomes in patients post ABI. This is not to say therapeutic hypothermia should be completely disregarded, as evidence does exist of its benefit in patients with more severe, diffuse brain injuries (moderate evidence: BHYPO Post-hoc, Suehiro et al., 2015).

If therapeutic hypothermia is to be used, a few recommendations should be kept in mind (taken from https://braintrauma.org/):

1) Very mild (35-37°C) is just as effective as more intensive hypothermia protocols (32-34°C) at lowering ICP (Moderate evidence; BHYPO: Maekawa et al., 2015). There is conflicting evidence as to whether one temperature range is superior to the other at improving long term outcomes, however the strongest (moderate) evidence suggests they are both the same.

2) A long-term (120h) cooling protocol should be used in favour of a short-term (48h) intervention (moderate evidence; Jiang et al., 2006).

3) Intracranial/cerebral perfusion monitoring is as effective as brain tissue oxygenation monitoring when observing the effects on intracranial pressure (Moderate evidence; Lee et al., 2010).

4) Targeted hypothermia may be more effective than systemic hypothermia at improving ICP (limited evidence; Liu et al., 2006).

5) Combining hypothermia with an osmotic agent (ie. Mannitol) may provide superior ICP, cerebral perfusion and oxygenation control compared to hypothermia alone (limited evidence; Sun et al., 2016). A rebound of all parameters may be avoided by using a high dose (50g) mannitol.

Hyperventilation

Q6. What is one concern for prolonged hyperventilation following an ABI?

1. Metabolic acidosis

In general, there is limited evidence to support the use of hyperventilation as an intervention to lower elevated ICP post-TBI. Further, it has been reported that brief (40 min) periods of hyperventilation decrease cerebral blood flow and cerebral oxygen saturation, thus also calling into question the safety of this intervention.

International guidelines such as the Brain Trauma Foundation (Carney et al., 2017) and the Management of severe traumatic brain injury guidelines (Geeraerts et al., 2018) do not recommend hyperventilation/ hypocapnia (PaCO2 <30mmHg) as an effective treatment post TBI.

However, in a clinical setting there are some potential advantages for the use of hyperventilation in acute or hyperacute stages, specifically for blown pupils or for decompression.

8.5.1.2 Pharmacological Interventions

Osmolar therapies

Q7. What two osmolar therapies are regularly used in clinical settings, despite mixed evidence on their efficacy?

1. Hypertonic saline
2. Mannitol

Once again, there is limited evidence supporting the use of Hypertonic Saline (HTS) and/or mannitol in patients post ABI. Studies recommending its benefit in lowering ICP, increasing CPP, and increasing cerebral blood flow are retrospective in nature and lack proper controls. However, similar to other

interventions for acute ABI management, osmolar therapies are used regularly in a clinical setting. Typical dosing regimens are presented below.

Table 8.3 Typical Dosing Regimens of Osmolar Therapies

Therapy	Dosing Regimen
Hypertonic Saline	Dosing can range from 3-21% with 3% being the most common in practice. Hypertonic saline can be given as a continuous infusion or in intermittent boluses.
Mannitol	Typically given in doses ranging from 0.25-1.0 g/kg quarterly throughout the day (every 6-8 hours) with rapid infusion.

HTS has anecdotally been touted as the superior osmotic agent due to a better reflection coefficient and thus a tendency to cross the Blood Brain Barrier to a lesser extent. Upon analysis of the relevant literature however, there is inconclusive and limited evidence concerning whether HTS or mannitol is superior at lowering ICP. Furthermore, there is strong evidence that both are similar in terms of improving GOS-E scores post-discharge (Baker et al., 2009; Cooper et al., 2004; Vialet et al., 2003). These findings may be explained by the fact that blood brain barrier permeability is likely disrupted post TBI, resulting in the filtration of HTS and mannitol alike into the brain.

Clinical Tip!

If you are treating an individual with osmolar therapies be sure to remember to regularly monitor kidney function, serum osmolality, and electrolytes!

The Brain Trauma Foundation guidelines indicate that although hyperosmolar therapy may lower ICP, they do not recommend the use of any osmolar therapy due to the lack of evidence regarding long-term morbidity and mortality outcomes (Carney et al. 2017). On the other hand, the Management of severe traumatic brain injury guidelines strongly recommend the use of 20% mannitol or HTS (250 mOsm) for brief (15-20 min) periods of time to control elevated ICP or for patients with signs of brain herniation (Geeraerts et al., 2018). To conclude, the use of osmolar therapies have a strong foundation for their use in clinical settings and are used regularly in the acute stages of ABI.

Propofol

Q8. What is the mechanism of action for propofol? What are some common drug interactions with propofol?

1. Propofol is thought to inhibit the function of GABA through ligand-gated GABAA receptors
2. Common drug interactions include gaseous forms of anesthesia such as isoflurane and halothane, and opium related narcotics such as morphine, meperidine, and fentanyl.

A review of pharmacological interventions post ABI by Alnemari et al. (2017) noted that propofol should be the sedative of choice in patients with TBI. Propofol has a rapid onset and displays short-term benefits with regards to protection against cerebral edema and subsequent ischemia. While effects on cerebral oxygenation appear to be minimal, the main benefits lie in its ability to reduce ICP. However, in the

literature meeting ERABI inclusion criteria there is limited evidence that propofol can lower ICP and improve CPP in patients post ABI. More convincing evidence has been found when propofol is used in combination with other sedatives or analgesics. For example, there was moderate evidence that when used in combination with morphine, propofol was able to more effectively lower ICP post TBI (Stewart et al., 1994).

The Brain Trauma Foundation guidelines make Level IIB recommendations recommending propofol for the control of ICP, although it does not show improvements in mortality or 6-month outcomes. The guidelines also cautioned the use of high-dose (> 5mg/kg/hr, or any dose >48h) propofol because of significant morbidity (Carney et al. 2017).

Barbiturates

Q9. What are some of the side effects of barbiturate use?

1. Immunological suppression, hypotension, skin rashes, nausea, fainting, and liver damage.

A review by Alnemari et al. (2017) concluded that induction of a barbiturate coma could reduce ICP refractory to standard therapy; however long-term outcomes were noted to be worse compared to individuals who did not receive barbiturates.

Based on the literature reviewed, there is conflicting evidence as to whether pentobarbital is more effective than standard therapy at improving ICP post ABI (moderate evidence from; Eisenberg et al., 1988; Ward et al., 1985). Further, there is moderate evidence that thiopental is superior to pentobarbital at improving ICP refractory to standard treatment. However, in North America pentobarbital is typically used as there is limited access to thiopental. If thiopental is to be used a suggested dosage example is given as: 2-20mg/kg loading dose, 3-6 mg/kg/h maintenance dose (Alnemari et al., 2017). Similar to the other interventions evaluated for ICP management, barbiturates are typically used in acute clinical settings.

The Brain Trauma Foundation guidelines recommend the use of high-dose barbiturates to control elevated ICP "refractory to maximum standard medical and surgical treatment" (Carney et al. 2017). The potential hypotensive complications were also taken into account, as the guidelines recommend vigilant surveillance of hemodynamic stability throughout barbiturate therapy (Carney et al. 2017). The SFE guidelines make similar recommendations of careful hemodynamic surveillance.

Given the significant side-effect profile of barbiturates, including immunological suppression and systemic hypotension, all interventions, including surgical treatments, should be attempted before utilizing barbiturates to control refractory intracranial hypertension.

Cannabinoids

Based on the literature reviewed, moderate evidence exists both supporting the use of Dexanabinol, (Firsching et al., 2012; Knoller et al., 2002) and reporting no benefit of Dexanabinol, (Maas et al., 2006) as a synthetic cannabinoid used to decrease ICP, increase CPP, and improve morbidity and mortality outcomes post ABI. In a study examining the synthetic product KN38-7271, the observed benefit was most prominent at higher (1000 µg) compared to lower (500 µg) doses. While the effect of Dexanabinol is unclear, the therapeutic potential of KN38-7271 is intriguing. KN38-7271 functions as a CB-1 and CB-2 receptor agonist, different than the NMDA-antagonistic effects of dexanabinol, and may be effective at doses an order of magnitude lower than dexanabinol. Information on dexanabinol can be found here (https://pubchem.ncbi.nlm.nih.gov/compound/Dexanabinol).

In a review by Farrell & Bendo (2018), the authors discussed dexanabinol in the context of recent Phase 1 and 2 trials that demonstrated improved neurological outcomes in patients post TBI. The positive results from these preliminary studies show promise in the use of this agent as an intervention to improve neurological and morbidity outcomes, and have encouraged the conduct of a larger trial that is currently underway.

Currently, there are no guideline recommendations regarding the use of cannabinoids in the management of patients with ABI.

Given the current research landscape and lack of formal recommendation by international guidelines, cannabinoid agents are not recommended for use in ICP management post TBI.

8.5.1.3 Surgical Interventions

Cerebrospinal Fluid Drainage

Q10. What types are drains are recommended by multiple brain injury guidelines?

1. External ventricular drains

Based on the literature reviewed, there is moderate evidence that ventricular drainage temporarily (<24h) lowers elevated ICP, and increases cerebral blood flow and perfusion pressure post TBI. This therapeutic benefit was noted independent of CSF volume drained, however was more pronounced at higher volumes (1-3 mL, Kerr et al., 2001). Further, there is moderate evidence that continuous drainage may be superior to intermittent drainage at lowering ICP. There is evidence that lumbar CSF drainage is effective at lowering ICP as well, especially in patients with intracranial hypertension refractory to standard ICP treatment, however, evidence supporting this is limited.

Key Study

Author/Year/ Country/ Study Design/N	Methods	Outcomes
Lescot et al. (2012) France Pre-Post N=20	**Population:** TBI; Median Age=49yr; Gender: Male=14, Female=6; Median GCS=8. **Intervention:** Participants received ventricular CSF drainage. **Outcome Measures:** Intracranial Pressure (ICP), Cerebral Perfusion Pressure (CPP).	1. Mean ICP significantly decreased at 12hr and 24hr when compared to pre-treatment ($p<0.05$). 2. Mean CPP significantly increased at 12hr when compared to pre-treatment ($p<0.05$).

The Brain Trauma Foundation guidelines made two level III recommendations regarding external ventricular drainage (EVD): Continuous drainage of the CSF at the mid brain may lower ICP more effectively than intermittent use, and 2) CSF drainage should be considered in the first 12 hours in patients with a GCS < 6 (Carney et al. 2017).

The Management of severe traumatic brain injury guidelines make similar recommendations, noting that drainage of a small volume of CSF markedly reduces ICP (Geeraerts et al., 2018). The guidelines go on to list 5 indications to performing EVD in the early phases of treatment.

Decompressive Craniectomy

Q11. What are the Benefits and Drawbacks of Decompressive Craniectomies in Reducing ICP

1. Reduced mortality
2. Greater long-term disability

Based on the literature reviewed, there is strong evidence that Decompressive Craniectomies (DC) can effectively reduce ICP, albeit at the cost of poorer long-term outcomes compared to standard therapy. Decompressive craniectomies represent a tradeoff between mortality and poor outcomes, overall more individuals survive their traumatic injuries, however, they have overall greater long-term disability.

Reports of high mortality are common in the literature (De Bonis et al., 2011; Eberle et al., 2010), however the largest trial yet (RESCUEicp trial; Hutchinson et al., 2016) reported a decrease in mortality up to a year post-treatment. Overall, it is unclear if the higher rates of negative outcomes can be attributed to the intervention alone, or that patients selected for DC are inherently less stable and more prone to poorer outcomes. Recall, DC is usually performed in cases where ICP is refractory to all other treatments, alluding to the critical state of these patients prior to the intervention.

Certain factors that predict favorable outcomes have been identified in the literature, and include: younger age (Nambiar et al., 2015), earlier DC (Polin et al., 1997), and higher initial GCS score (Ho et al., 2011) but all are based on limited evidence. When comparing the size of DC moderate evidence exists supporting larger DC (12x15 cm unilateral fronto-temporo-parietal vs 6x8 cm temporo-parietal; Jiang et al., 2005; Qiu et al., 2009).

Debate also exists as to whether prophylactic removal of bone flaps (craniotomy) allows for greater ICP control or improved morbidity outcomes compared to a standard DC. There is limited evidence that both provide the same ICP control (Al-Jishi et al., 2011); however it is unclear which is superior at improving survival and long-term outcomes.

The Brain Trauma Foundation guidelines recognize that DCs can reduce ICP and minimize days spent in the ICU. The guidelines went on to make several Level IIA recommendations regarding DCs (Carney et al. 2017):

1) A Bifrontral DC is not recommended to improve outcomes (GOS-E scores, 6 mo) for patients with severe TBI with diffuse injury (no mass lesion), and with ICP elevation >20 mmHg for more than 15 min within a 1 hr period that are refractory to first-tier therapies.

2) A large (12 x 15 cm or 15 cm diameter) **fronto-temporo-parietal** DC is recommended over a small DC for reduced mortality and improved neurologic outcomes.

Further, the Management of severe traumatic brain injury guidelines suggest (based on weak evidence) to perform a DC to control ICP in the early phase of TBI when ICP is refractory to standard treatment (Geeraerts et al., 2018).

8.5.2 Prompting Emergence from Coma

8.5.2.1 Non-Pharmacological Interventions

Sensory Stimulation

Q12. What evidence supports the use of sensory stimulation to prompt emergence from coma?

1. Presently, there is only limited evidence that sensory stimulation may be effective, and only after several weeks of implementation.

The theory that sensory stimulation could enhance the speed of recovery from coma has gained traction as a viable treatment post ABI. Early studies focused on employing a single stimulus to a single sense (unimodal stimulation), whereas more current studies have focused on stimulating multiple senses using several stimuli (multimodal stimulation). An example showcasing the potential benefits of multimodal stimulation can be seen when studying the cognitive concept of attention. Attention, the concentration of awareness on an object, has been stipulated to focus more on multi-sensory than uni-sensory stimuli. Further, given that brain cortical processing is multi-sensory this type of stimulation may better engage areas of higher cortical functioning- thus improving emergence from coma (Abbate et al., 2014; Padilla & Domina, 2016). Some of the senses that have been investigated to improve consciousness include: visual, auditory, tactile, olfactory, gustatory, kinesthetic, proprioceptive, and vestibular.

Sensory stimulation studies are difficult to summarize, given the different possible combinations of senses stimulated and protocols implemented. However, a recent review found strong evidence that multisensory stimulation can improve arousal from a coma and can enhance clinical outcomes (Padilla & Domina, 2016). The authors recommended early, frequent, and sustained stimulation that uses familiar stimuli tailored specifically to the individual in question. The below table summarizes the evidence associated with the stimulation of single, or multiple senses.

Table 8.4 Sensory stimulation techniques intended to promote emergence from coma

Sensory stimulation	Description	Reference
Auditory	Stimulation included orientation and commands, bells, blocks & claps, music, familiar voices, and television or radio. Each intervention lasted 5-15min, 5-8x/d, for up to 7d. Functional improvement was variable, with improvements noted on certain recovery scales (DRS, SSAM) but not others (GCS) compared to controls. Recent evidence suggests increased improvement if stimuli is a family member's voice, or the sound of the patient's name (moderate evidence).	Davis & Gimenez, 2003; Tavangar et al., 2015
Tactile	Limited evidence that tactile stimulation with biographically meaningful objects transiently improves motor behaviours in patients with TBI with DOCs.	Di Stefano et al., 2012
Multi-modal	There is strong evidence that multisensory stimulation delivered for 1-2 weeks is more effective than standard care at improving consciousness and cognitive function post ABI. Stimulation delivered frequently (5x/d) and by family members may maximize treatment benefits (moderate evidence).	Abbasi et al., 2009; Megha et al., 2013; Moattari et al., 2016

Currently, none of the guidelines reviewed (Carney et al., 2017; Geeraerts et al., 2018; National Clinical Guideline Centre, 2014; Giacino et al., 2018) review make any recommendations regarding sensory stimulation in improving DOC post ABI. However, as this intervention is non-invasive and relatively low-risk it may be attempted when appropriate in acute settings.

Electrical Stimulation

The median nerve plays a large role in maintaining normal motor and sensory function in the forearm and the hand. More specifically, part of the function of the median nerve is the transmission of cutaneous sensation over the lateral three and a half digits, predominately on the palmar side, and the innervation of the thenar muscles of the hand to provide mobility to the first digit— i.e., the thumb (Murphy, 2019; Padilla & Domina, 2016). Given the disproportionate representation of the hand in both the somatosensory and primary motor cortex, median nerve stimulation is thought to recreate electrical activity over a large area of the brain, analogous to the activity generated with the movement of the hand. This brain activity is postulated to elevate dopamine levels in the brain, presumably also increasing dopamine levels in the ARAS, and potentially stimulating wakefulness in a comatose patient (Cooper & Cooper, 2003).

Based on the literature reviewed, conflicting evidence exists regarding the benefits of median nerve stimulation in patients post ABI. While there is some limited evidence of improvements in consciousness, arousal, CPP and dopamine levels (Lei et al., 2015), the strongest (moderate) evidence suggests no benefit (Peri et al., 2001). It is important to note that the study by Perri and colleagues only had a follow-up period of 3 months, and previous studies have mentioned improvements in consciousness only appreciable at 6 months.

Currently, none of the guidelines reviewed (Carney et al., 2017; Geeraerts et al., 2018; National Clinical Guideline Centre, 2014; Giancino et al., 2018) review have made any recommendations regarding sensory stimulation in improving DOC post ABI.

8.5.2.2 Pharmacological Interventions

Amantadine

Q13. What is the only pharmacological intervention supported by American Academy of Neurology's practice guidelines (2018 update) to improve recovery in traumatic DOC? What is the recommended dosage?

1. Amantadine
2. 100-200 mg twice daily.

Amantadine is a dopamine agonist that acts both pre- and post-synaptically to upregulate dopamine activity (Vella et al., 2017). Dopamine is thought to be involved in frontal lobe stimulation and plays a role in behavior, mood, language, motor control, hypothalamic function and arousal (Lazaridis et al., 2018). Most importantly in the context of DOCs, increasing dopamine activity is postulated to increase activity at the ARAS, thus improving wakefulness and consciousness (Cooper & Cooper, 2003). Researchers believe that amantadine could significantly improve arousal in patients who are comatose.

Based on the literature reviewed, there is strong evidence that amantadine improves consciousness, cognitive function and disability compared to placebo post ABI (Giacino et al., 2012; Meythaler et al., 2002). Interestingly, the therapeutic benefits of amantadine appear to be present only during periods of drug administration, as recovery from coma is identical to placebo groups after a wash-out period (Giacino et al., 2012).

Despite strong evidence supporting amantadine, currently neither the Brain Trauma Foundation guidelines (Carney et al., 2017), Management of severe traumatic brain injury guidelines (Geeraerts et al., 2018), or the NICE guidelines (National Clinical Guideline Centre, 2014) make any recommendations regarding amantadine administration for improving DOCs post ABI.

The Practice Guideline Update Recommendations Summary: Disorders of Consciousness make a recommendation of amantadine administration to improve recovery in patients with TBI with a DOC, however the recommendations were made for patients in the subacute (4-16 wk post injury) phase (Giancino et al., 2018).

8.5.3 Interventions Focused on LOS, GCS, GOS, and Mortality

8.5.3.1 Non-Pharmacological Interventions

Rotational therapy

Initiating physical rehabilitation simultaneously to standard ICU care has gained traction as a safe and viable combination to reduce physical deconditioning, improve circulation, reduce ventilator dependence/ complications, and improve arousal in patients post ABI (Andelic et al., 2012; Malkoc et al., 2009). Given the lack of voluntary control in patients with a DOC, mobilization of an individual on a tilt-table or a generic mobilization protocol conducted by a physical therapist are examples of interventions that encourage patient mobility without requiring conscious control. Verticalization on a tilt table in particular, can stimulate sensory pathways and postural reactions to improve arousal and wakefulness from coma (Frazzitta et al., 2016).

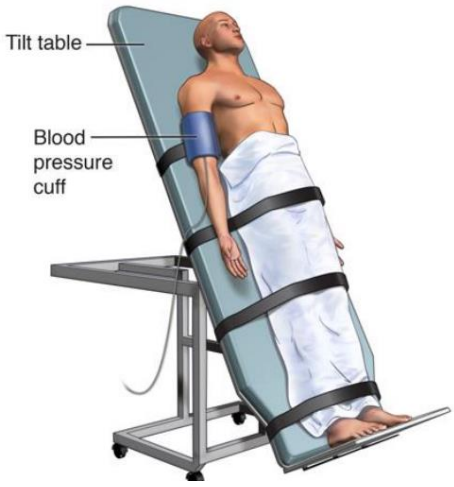

Figure 8.3 An example of the type of tilt table which may be used for therapy (taken from http://edmontoncardiology.com/tilt-table.php)

Based on the evidence reviewed, there is limited evidence that conventional physiotherapy alone, or in combination with verticalization, can improve long-term outcomes (GCS, DRS scores) post ABI. The safety profiles of these interventions are paramount, given the potential to precipitate a hypotensive episodes or periods of brain ischemia. There is limited evidence that verticalization using the Erigo (tilt table with integrated leg movements) causes less sympathetic stress, and is thus safer compared to standard verticalization using the MOTOmed machine or standard physiotherapy alone.

Currently none of the guidelines reviewed (Carney et al., 2017; Geeraerts et al., 2018; National Clinical Guideline Centre, 2014; Giacino et al., 2018) make any recommendations for or against rotational therapy for treatment post ABI.

Intracranial Pressure Monitoring

In systematic review by Yuan et al. (2015) concluded that despite recommendations by major guidelines and regulatory bodies, there was no evidence that ICP monitoring decreased the risk of death in patients post TBI. However, hospital and ICU length of stays tended to be significantly shorter for those receiving ICP monitoring.

This conclusion is in accordance with the literature published at that time, where there is moderate evidence that invasive ICP-monitoring interventions had similar morbidity and mortality outcomes as imaging/clinical based monitoring interventions (BEST TRIP; Chesnut et al., 2012). In the time since the landmark BEST TRIP study was published, there has been a shift in the literature regarding the relationship between ICP monitoring and patient outcomes. Recently studies have tended to report decreases in mortality associated with invasive ICP monitoring (Agrawal et al., 2017; Yuan et al., 2015).

Clinical Tip!

According to the French SFE guidelines the following are the strongest indicators of raised ICP

- Disappearance of cerebral ventricles
- Brain midline shift over 5 mm
- Intracerebral hematoma V over 25 mL
- Compression of basal cisterns (top sign)

It is important to mention that moderate evidence exists suggesting that non-invasive ICP management results in increased frequency and number of ICP-lowering interventions. The increased intervention frequency may be due to increased clinician suspicion of raised ICP, which develops in the absence of a discrete ICP value to guide treatment. Presumably, this increase in interventions could predispose an individual to higher rates of complications, however there were no reported outcomes to support this.

Key Study

Author/Year/ Country/Study design/PEDro Score	Methods	Outcome
Chesnut et al. (2012) Bolivia& Ecuador BEST:TRIP Study RCT PEDro=8 N=324	**Population:** TBI=200. *Pressure-monitoring group (n=157)*: Median Age=29yr; Gender: Male=143, Female=14. Median motor GCS score=5. *Imaging-Clinical Examination (ICE) group (n=167)*: Mean Age=29 yr; Gender: Male=140, Female=27, Median motor GCS score=4. **Intervention:** Patients were randomly assigned to either the ICP-monitoring, or the imaging and clinical examination (ICE) group. Patients in the ICP-monitoring group had an intraparenchymal monitor placed as soon as possible. Patients in the ICE group were treated in accordance to hospital protocol. Outcomes were assessed at discharge, 3 and 6 mo. **Outcomes:** Survival, Duration and Level of Impaired Consciousness, Functional Status and Orientation (3mo-GOSE, DSR, GOAT), Functional and Neuropsychological Status (6 mo), Hospital Length of Stay, Systemic Complications.	1. There were no significant differences between the groups in survival, 14 d or 6 mo mortality, hospital LOS, incidence of neurological worsening. 2. Patients in the pressure-monitoring group had a significant higher rate of decubitus ulcers compared to the ICE group (p=0.03) 3. The median interval during which patients received brain-specific treatment, total number of treatments, use of high dose barbiturates, and proportion of patients treated with HTS or hyperventilation was significantly higher in the ICE group (p=0.05)

Major organizations such as the Brain Trauma Foundation have modified their ICP monitoring guidelines based on more stringent inclusion criteria, removing previous indications for invasive ICP monitor use. However, overall there is near consensus amongst guidelines recommending the use of ICP monitors to guide treatment.

The Brain Trauma Foundation guidelines make Level IIB recommendations regarding the use of ICP monitoring to reduce in-hospital and 2-week post-injury mortality (Carney et al. 2017).

The French SFE guidelines make grade 2+ recommendations for monitoring ICP to detect intracranial hypertension in specific cases: Signs of high ICP on brain CT scan, extracranial surgical procedures, neurological evaluations not feasible.

The Australian NSW guidelines make grade A recommendations regarding the use of ICP monitoring to guide management of CPP.

Guideline implementation

Adherence to TBI management guidelines, such as those produced by the Brain Trauma Foundation, are generally low and variable (30-65%) across centers despite general agreement that they are evidence-based and necessary for providing best care (Cnossen et al., 2016; Gupta et al., 2016). Low adherence rates are concerning as studies have found a correlation between guideline adherence and patient outcomes (English et al., 2013). A number of barriers stand in the way of the optimal adherence, with one of the most commonly cited being the discrepancy in resources between the nations creating the guidelines (i.e. high-income countries) and certain nations attempting to implement them (i.e. middle-low income countries; (Agrawal et al., 2012; Cnossen et al., 2016). The discrepancy in resources and infrastructure, which lead to suboptimal guideline implementation, is particularly concerning given that the highest rates of TBIs, and thus the greatest need for proper TBI care, have been reported in middle-lower income nations (Dewan et al., 2018; Hyder et al., 2007; Patel et al., 2016).

While resource discrepancy may explain low adherence rates in a subset of nations, it does not account for this phenomenon in Western nations. Literature on adherence rates in these nations have reported section-specific differences in guideline uptake, primarily based on strength of recommendation/ perceived amount of evidence behind the recommendation (Lei et al., 2013; Saherwala et al., 2018). Clearly illustrating this phenomena, Cnossen et al., (2016) reported that out of all of the reviewed guidelines, the NICE CT guidelines have the highest adherence rates whereas the BTF ICP monitoring guidelines, known to be limited by a lack of prospective data, have the lowest.

While one study has shown that there are no mortality benefits noted with adherence rates above 60% (Gupta et al., 2016), care centers should strive for guideline adherence, guideline implementation, and the modification of existing protocols to improve uniformity and standard of care for individuals with ABI.

8.5.3.2 Pharmacological Interventions

Osmolar therapy

Q14. Which guidelines recommend the use of osmolar therapies for long-term outcomes following an ABI?

1. None. Unfortunately, due to inconclusive evidence no guideline groups to our knowledge recommend the use of osmoloar therapies. However, individual benefits have been anecdotally demonstrated and osmolar therapies are used regularly in clinical settings.

This section focuses exclusively on the functional and mortality outcomes associated with different osmolar therapies. For the effect of these interventions on ICP, please refer to section 8.5.1.2.

Based on the literature reviewed, there is moderate evidence that 4% albumin administration increases mortality in patients with ABI, especially those with severe (GCS<9) injury (Myburgh et al., 2007). Notably, there was no effect on GOS-E scores 2 years post-treatment.

Further, the efficacy of HTS (7.5%) saline was once again called into question in terms of its benefits on long-term outcomes when a study by Baker at al. (2009) reported no benefits in GOS, GOS-E, FIM, or DRS scores when HTS (7.5%) + Dextran (6%) administration was compared to normal (0.9%) saline infusions.

Another commonly used hyperosmolar agent is mannitol. There is moderate evidence that mannitol increases the risk of hypotension through increased urine output, however it has the same effect on mortality as hypertonic saline post ABI (Sayre et al., 1996).

The Brain Trauma Foundation guidelines indicate that although hyperosmolar therapy may lower ICP, they do not recommend the use of any osmolar therapy due to the lack of evidence regarding long-term morbidity and mortality outcomes (Carney et al. 2017).

The Management of severe traumatic brain injury guidelines do not recommend using 4% albumin in patients with TBI (Geeraerts et al., 2018).

Corticosteroids

Conflicting evidence regarding the benefits of corticosteroids in long-term survival and functional improvement for those with an ABI has been reported in numerous studies. The most definitive evidence arose after Roberts and colleagues performed a large, multi-center randomized study (Roberts et al., 2004) that was terminated early due to a calculated relative mortality risk of 1.8 (p=0.0001). From that trial on, the use of corticosteroids has been halted in the TBI population and guidelines have strongly advised against their use.

Although steroids are no longer used in practice to improve long-term mortality outcomes, it is important to remember they should still be considered when situations indicating their intended use arise. For example, there is limited evidence outlining a survival benefit after methylprednisolone administration (3

days, 500 mg/day) in patients with sepsis and acute respiratory distress syndrome secondary to severe TBI (Oliynyk et al., 2016).

The reviewed guidelines do not recommend the use of steroids to lower ICP or improve morbidity and mortality outcomes in patients with ABI.

Non-traditional pharmacological agents

The following table includes a list of pharmacological interventions that have been evaluated for the treatment of ABI. These interventions include progesterone, Erythropoietin, tranexamic acid and propranolol.

Table 8.5 Evidence of non-traditional pharmacological agents' effects on outcome parameters.

Intervention	Description	Reference
Progesterone	Animal studies have noted neuro-protective effects following brain injury (reduction of vasogenic edema, secondary neuronal death, free radical formation). There was strong, unanimous evidence that progesterone is the same as placebo at improving GOS scores up to 3 mo after treatment. Subgroup analysis of Shakeri et al. (2003) suggested benefit in GCS 5-8 patients, however other studies reported serious complications such as phlebitis and thrombophlebitis (Wright et al., 2014)	Shakeri et al., 2013; Wright et al., 2014; Skolnick et al., 2014
Erythropoietin	Postulated to serve as a neuroprotective agent, improving morbidity and mortality post TBI. A large multi-center RCT in 2015 concluded there was no difference in the rate of complications, morbidity, or mortality outcomes compared to placebo. A secondary analysis suggested it may improve mortality in patients who had previously undergone a neurosurgical procedure.	Nichol et al., 2015; Skrifvars et al., 2017
Tranexamic Acid (TA)	Intracranial hemorrhage (ICH) is a devastating secondary complication of TBI. Anti-fibrinolytic therapy use post TBI was proposed to decrease the risk/progression of ICH, thus improving recovery and survival. ICH growth was significantly slowed in patients receiving TA + standard care vs TA + placebo. Further studies on mortality and functional outcomes are required.	Jokar et al., 2017
Propanolol	β-Adrenergic receptor blockers mediate anti-inflammatory properties which can be neuroprotective post TBI. Propanolol in particular can penetrate the blood brain barrier and provides non-selective inhibition. A recent case-control study noted a decrease in mortality, albeit at the cost of greater number of days on a ventilator. Further studies with a randomized design, and investigating functional outcomes are required.	Ko et al., 2016

A meta-analysis for progesterone intervention showed no significant improvement on functional recovery or mortality post TBI (Wang et al., 2016). Tranexamic acid was noted to limit ICH progression (Zehtabchi

et al., 2014) free of vasculo-occlusive events, however its benefits on clinical outcomes and mortality remain unclear (Ker et al., 2013; Marehbian et al., 2017). The most promising of the interventions reviewed was propranolol, with a meta-analysis noting a significant reduction of in-hospital mortality (Pooled OR= 0.39, 95% CI: 0.27-0.56; p<0.001; Alali et al., 2017). Recommendations for the implementation of routine beta-blocker administration would be premature, however, as its association with cardiopulmonary adverse events and functional outcomes have to be further elucidated.

No guidelines to our knowledge recommend the use of any of the aforementioned interventions.

8.6 Case Study

Patient Snapshot:

Liam
Is a 24-year-old male who sustained a TBI after falling from a fourth-floor apartment balcony. The fall is witnessed by bystanders and he is transported to a major trauma centre via ambulance. On arrival to the emergency department he is agitated, combative and vomiting. However, he is able to open his eyes in response to speech, utter random words, and withdraw from painful stimuli. His vital signs are as follows: heart rate=28 bpm, blood pressure=221/105 mm Hg, respiratory rate=16/min, temperature=36.5°C.

Q1. Based on the GCS, what is the patient's eye opening, verbal response, motor response and total score?
Eye – 3; Verbal – 3; Motor – 4
GCS = 10

Q2. Which clinical features are highly suggestive of intracranial injury?
- Mechanism of injury
- Reduced GCS score
- Vomiting
- Agitation
- Aggression

While Liam was initially able to protect his airway, his condition is rapidly deteriorating and he is moved onto his side for secretion suctioning. What are the next steps for stabilizing the patient's airway?

Perform a rapid sequence endotracheal intubation to protect the patient's airway and facilitate further investigations. This process involves preoxygenation and induction with a sedative (e.g., propofol), analgesic (e.g., fentanyl), and paralytic (e.g., rocuronium).

While Liam's airway is being stabilized, what are the next steps for fluid and medication administration?

1. Extensive bloodwork for investigation
2. Establish two large bore (14-16 G) intravenous catheters for fluid and medication administration. 7
3. Administer atropine and nicardipine infusion for improvement in heart rate and blood pressure, respectively.

Case Continued
Liam is transferred directly from the emergency department to the CT scanner. Imaging showed an extensive fracture through the right temporal bone. An acute traumatic subdural hematoma overlaid the right cerebral cortex with subarachnoid blood. A moderate midline shift of 5.5 mm was demonstrated. Contrecoup hemorrhagic contusions were present on the left temporal lobe. Right-sided herniation was present. No evidence of fracture or dislocation of the C-spine.

Q3. Describe the principle diagnoses.
Subdural hematomas are the result of bleeding from bridging veins which cross through the subdural space. Collection of blood in this space is typically the result of assault or falls. Blood can also pool in the subarachnoid space between the arachnoid and pia mater. Brain herniation is the result of brain tissue shifting from one space to another through folds and openings. After a brain injury, it occurs from internal bleeding or swelling.

Q4. How is increased ICP destructive to the brain?
Elevated ICP secondary to edema, mass lesions, or hemorrhage can have a devastating effect on the brain. The ischemic environment created by the occlusion of cerebral vessels can impair focal or global circulation in the brain, depending on the insult, resulting in hypoxia and cell death.

Given Liam's herniation syndrome and elevated ICP, what emergent treatment options are available?

Surgical

- Employ physical interventions to reduce ICP by either decreasing the volume of fluid (blood, CSF) or increasing the size of the cranial compartment (i.e., decompressive craniectomy)

Non-Surgical (Pharmacological):

- Focuses on reducing cerebral edema, decreasing metabolic demand, and maintaining adequate cerebral blood flow, and includes the use of both pharmacological agents (diuretics, corticosteroids, barbiturates, etc.) and non-pharmacological interventions (hypothermia, hyperventilation, head posture, body rotation, endotracheal intubation).

Case Continued
The patient underwent an emergency decompressive craniectomy, allowing brain swelling and ICP to decrease. He was also started on a continuous infusion of 3% NaCl and is maintained in a medically Induced coma.

Q5. After surgery, where should the patient be transferred?
He should be transferred to the intensive care unit for continued medical management and monitoring. ICP and CPP should be managed via ventilatory and pharmacological strategies.

Q6. To promote the best possible outcome, what thresholds for ICP and CPP should be maintained?
- ICP: ≥22 mm Hg
- CPP: 60 – 70 mm Hg

Q7. What would you do to prompt this patient's emergence from coma?
Sedation should be weaned and the patient extubated so that neurological functioning can be assessed.

Case Continued
After waking from sedation, Liam has significant left-sided hemiplegia and aphasia. His GCS is now 12 (Eye-4, Verbal-2, Motor-6).

Q8. What are the next steps in Liam's recovery and rehabilitation?
After a prolonged stay in ICU, the patient should be stepped down to a neuromonitored ward and then discharged to a rehabilitation facility once he is medically stable.

8.7 References

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